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Analysis of Clinical Characteristics in Children with Severe Influenza A (H1N1)

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Abstract ***Objectives:*** To recognise the clinical features and therapeutic experiences of critical pandemic influenza A (H1N1) virus infection in children. ***Methods:*** During the two waves of pandemic H1N1 virus infection, 41 severely ill children infected with pandemic H1N1 virus were admitted to the paediatric intensive care unit of the Children's Hospital, Zhejiang University, School of Medicine. ***Results:*** The total mortality of two pandemic waves was 41.5% (17/41). A total of 92.7% of children had fever. A total of 27 children were intubated and supported with a mechanical ventilator. The factor of younger age was associated with higher mortality. The time on oxygen and respirator use was longer in deaths than survivals. The ratio of complications of septic shock, acute respiratory distress syndrome, and air leak syndrome was higher in deaths than survivals. ***Conclusions:*** Critical pandemic H1N1 virus infection in children less than 3 years old leads to high mortality, and early diagnosis and treatment is pivotal for successful treatment.

Key words Children; H1N1 virus; Pandemic

Introduction

Influenza A (H1N1) is an acute infection of the respiratory tract. In 2009 a novel H1N1 virus was discovered in Mexico and quickly spread to become a worldwide pandemic. From November 2009 to December 2011, there were two waves of pandemic H1N1 virus in Zhejiang province of China from November to December 2009 and January-March 2010. During the two waves, the paediatric intensive care unit (PICU) of the Children's Hospital, Zhejiang University, School of Medicine admitted 41 severely ill children infected with pandemic H1N1 virus.

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To enhance the recognition of severe pandemic H1N1 virus infection, the present study reports the clinical features and therapeutic experiences from the two pandemic waves.

Materials and Methods

General Information

During the first pandemic wave of November and December 2009, 33 children with severe infection of pandemic H1N1 virus were admitted to the PICU of the Children's Hospital, School of Medicine, Zhejiang University. These included 23 males and 10 females, with mean age of 3.7 years (range: 0.1-11.0 years), mean body weight of 14.8 kg (range: 3.4-38.0 kg), mean hospitalisation time of 19.2 days (range: 3.0-47.0 days), and mean time in the intensive care unit (ICU) of 10.5 days (range: 1.0-33.0 days). During the second pandemic wave of January-March 2010, eight children with severe infection of pandemic H1N1 virus were admitted, including three males and five females. These children had a mean age of 4.6 years (range: 1.5-12.0 years), mean body weight of 20.3 kg (range: 10.5-58.0 kg), mean hospitalisation time of 21.9 days

(range: 2.0-41.0 days), and mean time in the ICU of 12.6 days (range: 2.0-34.0 days). None of the children had been vaccinated against pandemic H1N1.

Methods

The inclusion criteria for influenza were: clinical signs and symptoms of influenza, according to the Diagnosis/ Treatment Strategy of Influenza A (H1N1) (2009 Edition III and 2010 Edition) by the Chinese Ministry of Health, as well as either laboratory isolation of pandemic H1N1 virus or identification of pandemic H1N1 virus nucleic acid. Besides the typical influenza signs of fever and cough, other atypical features includes low grade fever, lack of alertness, tachypnoea, labored breathing, cyanosis and central nervous system involvement. All children in this study met the diagnostic criteria of critical cases and were complicated with at least one of the following: respiratory failure, septic shock, multiple organ dysfunction, and other severe clinical conditions requiring monitoring.

Statistical Analysis

Statistical analysis was performed with SPSS15 software. Categorical data were expressed as cases (percentage) and analysed with the Rank test. Continuous data were expressed as median (minimum-maximum) and analysed with χ^2 test. $P<0.05$ or 0.01 was considered significant.

Results

During the first wave, 20 children survived and 13 children died. During the second wave, 4 children survived and 4 children died. The total mortality of the two pandemic waves was 41.5% (17/41).

A total of 92.7% of children had fever; 31 children had fever >39°C including 8 children with fever >40°C. The duration of fever was >3 days in 37 of the children, with a maximum of 14 days in one child. The children had obvious signs of respiratory disease, with cough, tachypnea and hypoxia, and were oxygen dependent and a higher oxygen concentration. A total of 27 children required supportive treatment with an artificial respirator through a trachea cannula. Nine children incurred neural signs like coma and convulsion at the early stage of fever. Seven children exhibited repetitive convulsions and vomiting, while two children were admitted to the hospital because of coma and were diagnosed with pandemic H1N1 because of fast progression of clinical disease. Twelve children had underlying diseases, including four children undergoing chemotherapy for leukemia or postoperative tumor. Three children had diseases of the nervous system, including two children with epilepsy and one child with spinal muscular atrophy. Three children had congenital heart disease. One child had asthma and one child had mycoplasma pneumonia. The cases with underlying disease had more complications such as acute respiratory distress syndrome (ARDS), septic shock, and hepatic function damage (Table 1).

To investigate risk factors for death in severe pandemic H1N1 virus infections of children, we compared the clinical features between deaths and survivals. The results indicate that mortality is higher in children who are younger. The time on oxygen and respirator use was longer in deaths than survivals. The ratio of complications of septic shock, ARDS, and air leak syndrome was higher in deaths than survivals (Table 2).

Table 1 Clinical features and complications in H1N1 children

Signs	2009 (n=33)	2011 (n=8)	Total (n=41)	Incidence rate (%)
Fever (>38°C)	30	8	38	92.68
Cough	31	6	37	90.24
Nervous system signs: coma, convulsion	7	2	9	22
Underlying diseases	9	3	12	29.3
Acute respiratory distress syndrome	13	5	18	43.9
Shock	11	5	16	39.0
Liver and kidney dysfunction	10	2	12	29.3
Air leak syndrome	13	5	18	43.9

Discussion

Fever, cough, and tachypnoea are the major clinical features in children infected with the pandemic H1N1 virus. Some children can incur nervous system signs such as coma and convulsion, which can lead to misdiagnosis as viral encephalitis. Therefore, for children with nervous system signs during an influenza epidemic, a specimen should be collected to investigate a possible influenza diagnosis.

Severe pandemic H1N1 virus infection has a higher morbidity of ARDS and mortality than seasonal influenza.[1] The basis for refractory hypoxia in children with severe pandemic H1N1 virus infection is the widespread inflammatory consolidation of the lung, mismatch of the ration of ventilation and blood flow in the lungs, and the thickness of the alveolar capillary membrane. These pathological changes result in the disorder of oxygen distribution. If the child has obvious signs of dyspnea requiring high-concentration oxygen to maintain a normal partial pressure of oxygen, early application of non-invasive or invasive positive pressure ventilation should be applied to prevent fatigue and failure of respiratory muscles.

Table 2 Comparison of clinical features between deaths and survivals

Items	Dead cases (n=17)	Live cases (n=24)	*P* value
Gender (M/F)	9/8	17/7	0.241
Age [M(min-max),y]	3 (0.2-7)	4.5 (0.1-12)	0.034[a]
ICU time [M(min-max),d]	11 (1-34)	9.5 (1-17)	0.185
Oxygenation time [M(min-max),d]	12 (3-38)	8.5 (2-21)	0.029[a]
Respirator use time [M(min-max),d]	11 (0.5-33)	2 (0-12)	0.000[b]
Hospitalisation time [M(min-max),d]	21 (3-43)	16 (6-47)	0.711
Fever [M(min-max),°C]	39.3 (37.5-40)	39.6 (37.7-41.4)	0.442
Air leak syndrome (cases, %)	11 (64.71)	7 (29.17)	0.024[a]
ARDS (cases, %)	13 (76.47)	5 (20.83)	<0.01[b]
Septic shock (cases, %)	10 (58.82)	6 (25)	0.029[a]
Function damage of liver and kidney (cases, %)	7 (41.18)	5 (20.83)	0.158

ICU=intensive care unit; ARDS=acute respiratory distress syndrome
Note: [a]$P<0.05$; [b]$P<0.01$; M(min-max): median(minimum-maximum)

In this study, 18 children were diagnosed with ARDS when admitted to the PICU, with the major sign being hypoxia. These children had very low oxygenation index, most under 200, and required high-concentration oxygen for a longer time, with a mean time of 12.2 days (range: 2.0-38.0 days). A total of 27 children (65.9%) failed to keep normal oxygenation with a nasal catheter, mask or non-invasive respirator, and underwent invasive mechanical ventilation. The rate requiring mechanical ventilation was lower than the study by Yung et al[2] who reported that 80% of children admitted to the ICU required mechanical ventilation. This difference may be related to different indications for respirator use. Supportive treatment with mechanical ventilation is not ideal for patients with wide lung consolidation, and related complications can contribute for more severe disease or death. Li et al[3] reported that in 24 cases of critical pandemic HIN1 virus infection, six cases required mechanical ventilation via trachea cannula, and there were five deaths. In the present study, 27 children were treated with a respirator for a mean time of 10.9 days (0.5-33.0 days), which is consistent with a report from Kumar et al[4] in Canada (12 days).

Lung air leak syndrome is an important imaging feature in critical pandemic H1N1 virus infection, demonstrated as pulmonary interstitial emphysema, mediastinal emphysema, pneumothorax, or subcutaneous emphysema to various extents. Lung air leak syndrome may be related to damage of the alveolar wall and necrosis of the bronchial wall.[5] Mechanical positive pressure ventilation can aggravate the risk of air leak to a certain extent. In the present study, 43.9% (18/41) children were treated with drainage because of pneumothorax. Eleven children had ≥2 drainage tubes placed; among them, three children each had three drainage tubes placed, and all three children died. All required the placement of drainage tubes for a long time (>7 days). To reduce the occurrence of air leak, a high-frequency respirator should be considered at an early stage. High-frequency oscillation ventilation can ventilate the lung evenly with higher pressure in the air tract, avoid stretching and shearing injuries of lung tissues, improve ventilation perfusion mismatch, correct hypoxia and hypercapnia, reduce incurrence of barotraumas, and prevent further damage of lung tissues. In the present study, nine children incurred a pneumothorax prior to the application of a respirator for high-frequency ventilation.

Critical pandemic H1N1 virus infection progresses quickly, particularly in children under 5 years old, and can easily develop into severe cases and severe complications in children under 2 years old.[6] In Argentina, 75% of children

with pandemic H1N1 virus infection were under 2 years old; within children who died, 85% of children were under 2 years old and 46% of children were under 1 year old.[7] A report from Singapore showed that the risk factors for complicated disease were comorbidity and age <2 years.[8] In the present study, younger children were prone to death; in the 17 deaths, 15 were under 5 years old and 7 were under 2 years old.

Multiple studies have indicated that children with underlying diseases are prone to pandemic H1N1 virus infection.[9,10] In one report of pandemic H1N1 virus infection in children from Germany, 75% of 93 children suffer underlying diseases, including neural development disorder, chronic respiratory disease, immune suppression, and heart disease.[10] Children with neural development disorders or chronic respiratory disease had higher mortality.[10] Torres et al[11] reported that the mortality of children in a PICU during the 2009 H1N1 pandemic reached 47%. In the 142 hospitalised children with confirmation of H1N1 virus infection, 7% children had underlying diseases. In the present study, 12 children (29.3%) had underlying diseases, and six (50%) of these died. A total of 29 healthy children quickly developed severe disease after infection with H1N1 virus and 11 children died, resulting in a mortality of 37.9%.

The morbidity of pandemic H1N1 virus infection lower in the 2011 wave than that of the 2009 wave, possibly related to asymptomatic infections during the 2009 pandemic and vaccination. However, mortality was still high in 2011. In the present study, the mortality was 42%, which is consistent with the 41% mortality reported from Mexico in 2009.[12] The mortality of critical pandemic H1N1 virus infection in children was 38% in the United Kingdom and 47% in Argentina.[11,13] Reports of mortality worldwide have varied widely. A report from WHO indicated that the mortality of critical H1N1 virus infection ranges from 14 to 46%.[14] Although in a single centre of Hong Kong from 2003 and 2009, Hon et al[15] reported low morbidity and no mortality of critical pandemic H1N1 in children, which was much lower than the results of ours and WHO, the critical pandemic H1N1 infection is a disease with high mortality, there is no effective specific treatment except administration of Oseltamivir at an early stage in the infection. The application of extracorporeal membrane oxygenation has been suggested for children infected with pandemic H1N1 virus.[16] Early diagnosis and treatment is still the key for successful treatment of critical pandemic H1N1 virus infection.

The United States Centers for Disease Control and Prevention confirmed bacterial infection in 22 of 77 deaths from pandemic H1N1 influenza, and considered complicated bacterial infection as an important factor resulting in aggravation of disease and death in the 2009 H1N1 pandemic.[17] In the present study two children who had recovered from the primary influenza infection and died from subsequent bacterial infection. Therefore, strategies like good isolation and infection control, prevention of secondary infection, can directly affect the prognosis. In addition, good disinfection and isolation is important for the prevention of influenza infection itself. In the present study, six children H1N1 infection were nosocomial acquired. To minimise hospital staff infection, it is recommended to receive pandemic H1N1 vaccine in addition to preventive strategies.

Declaration of Interest

None

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