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Pandemic 2009 influenza A (H1N1)-associated deaths among children in China: A retrospective analysis

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ABSTRACT

Importance: A cluster of influenza-associated deaths occurred among children during pandemic 2009 influenza A (H1N1) in China, but the risk factors and causes for death have not been clarified.

Objective: We describe the clinical findings regarding 2009 influenza A (H1N1)-associated pediatric deaths in China, including the risk factors for death.

Methods: The definition of 2009 influenza A (H1N1)-associated pediatric death is death in a child who is younger than 14 years and has laboratory-confirmed influenza. We collected data of total 810 hospitalized patients with 2009 influenza A (H1N1) infection from September 2009 to February 2010 in 17 hospitals across China. The clinical characteristics, laboratory abnormalities, and treatment course were retrospectively studied.

Results: Of the 810 patients hospitalized with 2009 influenza A (H1N1) infection, 19 (2.3%) died. Ten patients died from severe pneumonia and acute respiratory distress syndrome; eight died from encephalopathy/encephalitis; one died from secondary fungal meningitis. Patients who died were more likely than patients who survived to have neutrophilia, lymphopenia, elevated C-reactive protein, and elevations of lactate dehydrogenase, creatine kinase, creatine kinase-MB, aspartate aminotransferase and alanine aminotransferase. There were no significant differences in the median age, median time from onset of illness to admission, underlying chronic disease, and initiation of antiviral therapy within 48 hours of illness onset, between patients who died and those who survived.

Interpretation: The risk factors for pediatric death associated with 2009 influenza A (H1N1) infection are different from those of seasonal influenza. The most common causes of death are viral pneumonia, acute respiratory distress syndrome, and encephalopathy/encephalitis.

KEYWORDS

2009 influenza A (H1N1), Mortality rates, Children

INTRODUCTION

Since the emergence of the novel 2009 influenza A (H1N1) in March 2009, the world has witnessed its rapid and global spread to nearly all countries and territories.[1-3] The unique genetic and antigenic features of the 2009 influenza A (H1N1) virus have resulted in high morbidity and mortality, with a clinical spectrum and risk factors for mortality that are different from that of previous seasonal influenza infections. In contrast to seasonal influenza, more severe 2009 influenza A (H1N1) disease and related mortality have occurred among children and adults under the age of 64 years. During the 2009 influenza A pandemic, it was demonstrated that adults with underlying chronic diseases, and severe obesity as well as pregnant women are at increased risk for severe disease and death.[4] Although it is well known that age less than 5 years, and underlying chronic disease are risk factors for complications and death during epidemic seasonal influenza,[5] the data on risk factors of death in children during the 2009 influenza A (H1N1) pandemic is limited.

We conducted a multicenter retrospective investigation of children hospitalized with influenza A (H1N1) infection in China, during the outbreak in the winter of 2009. This report describes the clinical findings regarding 2009 influenza A (H1N1)-associated deaths, in which the causes of death and high-risk factors are different from that of previous reports.

METHODS

The definition of 2009 H1N1 influenza-associated pediatric mortality is death in a child who is younger than age 14 years and has a clinically compatible illness and laboratory-confirmed influenza H1N1 infection. We collected data of 810 patients hospitalized in 17 hospitals across China, during the 2009 H1N1 influenza A epidemic from September 2009 to February 2010. All 810 patients had confirmed 2009 H1N1 influenza A virus infection, detected using real-time reverse transcriptase polymerase chain reaction assay of nasopharyngeal swab specimens on admission. All 810 patients hospitalized of 2009 influenza A (H1N1) refer to selective testing, but not all hospitalized children were tested for H1N1 during the study period.

Clinical complications associated with 2009 influenza A (H1N1) virus infection included pneumonia, myocarditis, encephalopathy, or encephalitis within 5 days of influenza-like illness symptom onset, with no evidence of an alternative etiology. Pneumonia was diagnosed on the basis of the presence of infiltrates or consolidation on chest X-ray; hospital acquired pneumonia and ventilator associated pneumonia were excluded. Myocarditis was diagnosed on the basis of elevated creatine kinase (CK) and CK-MB, and evidence of decreased contractility

on echocardiography, arrhythmia, or an enlarged heart. Encephalopathy was defined as altered mental status lasting ≥ 24 hours. Encephalitis was defined as encephalopathy plus two or more of the following: fever ≥ 38.0 ℃, focal neurological signs, cerebrospinal fluid (CSF) pleocytosis, electroencephalogram (EEG) indicative of encephalitis, or abnormal neuroimaging indicative of infection or inflammation.[6]

A standard data-collection form was used by a pediatrician to collect data on the children hospitalized with 2009 influenza A (H1N1) infection. An independent reviewer subsequently checked the accuracy of the records. The standardized form included demographic data, clinical signs and symptoms, underlying chronic diseases, selected laboratory tests, radiographic findings, and treatment course.

We used two-class logistic regression analysis to calculate the ratio of various relevant factors and 95% confidence intervals for categorical variables as well as the nonparametric test of two independent samples for continuous variables. All analyses were performed with SPSS software, version 16.0 (SPSS Inc., Chicago, IL, USA). A *P* value of less than 0.05 was considered to indicate statistical significance.

RESULTS

In this multicenter retrospective investigation of hospitalized children with 2009 influenza A (H1N1) infection, 810 patients were included from 17 hospitals around the country, covering most large cities in China. Of the 810 patients with 2009 influenza A (H1N1) infection, 19 (2.3%) died. Selected clinical characteristics are presented in Table 1. Among the decedents, 11 (57.9%) were ages 9 months to 4 years, and eight (42.1%) were aged 5–14 years. Four (21.1%) patients had an underlying chronic disease; these were acute lymphoid leukemia (one patient), idiopathic nephrotic syndrome (one patient), hemolytic-uremic syndrome (one patient) and Down syndrome (one patient). No patients were obese. The most common presenting symptoms among the decedents were fever (100%), cough (100%), altered mental status (68%), dyspnea (58%), vomiting (53%), runny nose (42%), coma (26%) and seizures (26%).

Comparing the 19 patients who died with the 791 patients who survived, the decedents had significantly higher proportions of clinical complications, including pneumonia, acute respiratory distress syndrome (ARDS), encephalopathy/encephalitis, and myocarditis. However, no differences were found in the median age, sex distribution, underlying chronic diseases, median time from onset of illness to admission, and initiation of antiviral therapy within 48 hours of illness onset between patients who died and those who survived (Table 1).

Selected laboratory abnormalities in patients with 2009 influenza A (H1N1) infection are listed in Table 2. On admission, the most common laboratory abnormalities among decedents were elevated lactate dehydrogenase (LDH; > 225 IU/L; 89%), CK (> 175 IU/L; 79%), aspartate aminotransferase (AST; > 40 IU/L; 74%), CK-

TABLE 1 Comparison of clinical features of 2009 H1N1 influenza A

Characteristic	Died (N = 19)	Survived (N = 791)	Odds Ratio for Died (95% *CI*)	*P*
Age				
Median, mo (range)	49 (9–121)	43 (0.5–192)	–	0.55
≥ 5 Yr, N (%)	8 (42.1)	252 (31.9)	1.56 (0.62–3.92)	0.49
Male sex, N (%)	8 (42.1)	500 (63.2)	0.42 (0.17–1.06)	0.10
Median time from onset to admission (d)	5 (0–16)	5 (0–38)	–	0.71
Median length of hospital stay (d)	10 (1–46)	8 (1–91)	–	0.85
Underlying chronic disease, N (%)	4 (21.1)	144 (18.2)	1.20 (0.39–3.66)	0.75
Clinical complications, N (%)				
Pneumonia	19 (100)	567 (71.7)	1.40 (1.34–1.46)	0.00
ARDS	10 (52.6)	44 (5.6)	18.9 (7.29–48.8)	0.00
Encephalopathy/Encephalitis	13 (68.4)	36 (4.6)	45.4 (16.3–126.5)	0.00
Myocarditis	5 (26.3)	25 (3.2)	10.9 (3.66–32.8)	0.00
Corticosteroids treatment, N (%)	14 (73.7)	268 (33.9)	5.46 (1.95–15.3)	0.00
IVIG treatment, N (%)	12 (63.2)	193 (24.4)	5.31 (2.06–13.7)	0.00
Oseltamivir treatment within 48 hours, N (%)	3 (15.8)	160 (20.2)	0.74 (0.21–2.57)	0.63

ARDS, acute respiratory distress syndrome; IVIG, intravenous immunoglobulin G; CI, confidential interval.

TABLE 2 Comparison of laboratory test abnormalities of 2009 H1N1 influenza A

Characteristic	Died (N = 19)	Survived (N = 791)	Odds Ratio for Died (95% *CI*)	*P*
Leukocytosis, N (%)	6 (31.6)	187 (23.6)	1.49 (0.56–3.98)	0.42
Leukopenia, N (%)	6 (31.6)	177 (22.4)	1.60 (0.60–4.27)	0.34
Neutrophilia, N (%)	11 (57.9)	226 (28.6)	3.44 (1.37–8.66)	0.01
Lymphopenia, N (%)	12 (63.2)	225 (28.4)	4.31 (1.68–11.11)	0.00
Elevated C-reactive protein, N (%)	13 (68.4)	292 (36.9)	3.70 (1.39–9.85)	0.01
Elevated lactate dehydrogenase, N (%)	17 (89.5)	329 (41.6)	11.9 (2.74–52.0)	0.00
Elevated creatine kinase, N (%)	15 (78.9)	159 (20.1)	14.9 (4.88–45.5)	0.00
Elevated creatine kinase (CK)-MB, N (%)	13 (68.4)	135 (17.1)	10.5 (3.93–28.2)	0.00
Elevated aspartate aminotransferase, N (%)	14 (73.7)	243 (30.1)	6.31 (2.25–17.7)	0.00
Elevated alanine aminotransferase, N (%)	8 (42.1)	98 (12.4)	5.14 (2.02–13.1)	0.00

CI, confidential interval

MB (> 6.8 ng/ml; 68%), C-reactive protein (CRP; > 10mg/L; 8%), and elevations of alanine aminotransferase (ALT; > 40 IU/L; 42%). The incidence of neutrophilia, lymphopenia, and elevated CRP, as well as elevated LDH, AST, ALT, CK and CK-MB were higher in patients who died than in those who survived (Table 2).

Bacterial and fungal cultures were carried out in 18 patients who died; five had positive results for fungi in sputum; two had positive results for *Streptococcus pneumoniae* in sputum; one had positive results for Staphylococcus aureus in sputum; and one had positive results for fungi in pleural fluid and cerebrospinal fluid. All 18 patients had negative results for blood culture.

All 19 decedents were admitted to the intensive care unit (ICU), and all received antibacterial therapy before or on admission. A total of 15 (79%) decedents were treated with oseltamivir, within 48 hours in three (16%) of these patients. Patients who died were more likely than patients who survived to have received treatment with systemic corticosteroids or intravenous immunoglobulin G (IVIG) treatment (Table 1).

Among the 19 decedents, 10 died from severe pneumonia and ARDS, five of whom had complication of encephalopathy/encephalitis; eight patients died from encephalopathy/encephalitis; and one died from secondary fungal meningitis.

DISCUSSION

We describe a series of pediatric fatalities during the winter outbreak of 2009 influenza A (H1N1) in China. We included data of 19 fatal cases among 810 hospitalized patients. To our knowledge, this is the largest study of hospitalized children with 2009 influenza A (H1N1) infection. The childhood mortality rate (2.3%) in our case series is significantly lower than those of hospitalized adult patients in China (14.7% and 17.4%), although it is possible to overestimate, and comparable to 2.6% in the previous study.[7-9] These results indicate that the age-related mortality rate in China is consistent with findings reported elsewhere.[10-13] Whether there are differences in childhood mortality between patients with seasonal influenza A and those with 2009 pandemic influenza A (H1N1) has not been determined. Studies have shown that pediatric death rates associated with pandemic 2009 H1N1 influenza are much higher than those related to seasonal influenza in previous years in Argentina and the United States.[14-16] Comparable data on pediatric mortality associated with laboratory-confirmed seasonal influenza in previous years are unavailable in China. Many pediatricians observed a cluster of 2009 influenza A (H1N1)-associated deaths during the winter of 2009, when the pandemic of 2009 influenza A (H1N1) occurred in China. Therefore, national surveillance and reporting systems for influenza-associated deaths in children should be established in the future.

It is well known that children under the age of 5 years, adults 65 years of age or older, and persons of any age with underlying chronic diseases are at increased risk for complications and death owing to epidemic seasonal influenza. In contrast to seasonal influenza, 2009 influenza A (H1N1)-associated deaths predominately occur among individuals 18–64 years old.[10-12,17] For 2009 influenza A (H1N1), although pregnant women and patients with underlying chronic diseases and obesity remain at risk, some studies—including this report— have revealed that more deaths occur among previously healthy individuals.[8,9] Recent studies have shown that delayed diagnosis and nosocomial influenza A virus infection are also important risk factors for influenza mortality.[18,19] It is generally believed that bacterial infection can cause increases in leukocytes, neutrophils and CRP and decreased lymphocytes. However, most deaths in this study group lacked the basis for bacterial or other etiological infection,

suggesting that influenza A (H1N1) virus can also cause severe inflammatory response. The influenza A (H1N1) virus can also cause serious damage to the nervous system, digestive system and cardiovascular system. This study attempted to explore the risk factors for death among children with influenza A (H1N1), and we found that neutrophilia, lymphopenia as well as elevated CRP and elevated LDH, CK, CK-MB, AST, and ALT may be risk factors for death.

Consistent with findings in adult patients,[4,20] the complications of severe pneumonia and ARDS constituted the most frequent causes of pediatric death associated with 2009 influenza A (H1N1) infection in this study.[14,15,21] However, our findings revealed that encephalopathy/encephalitis associated with 2009 influenza A (H1N1) virus infection was also a most common cause of death among children, with 13 (68%) patients who had complications of encephalopathy/encephalitis; Eight (42%) patients died owing to encephalopathy/encephalitis. Influenza-associated acute encephalopathy/encephalitis has been well described in infection with seasonal influenza A or B viruses.[22-24] With regard to 2009 influenza A (H1N1) virus infection, a small number of patients with neurologic complications have been sporadically reported.[16,25-28] In this report, we describe a cluster of 2009 influenza A (H1N1)-associated encephalopathy/encephalitis cases with increased mortality, which are important to note by pediatricians.

Secondary bacterial or *Mycoplasma pneumoniae* infections have been demonstrated as an important factor contributing to deaths during pandemic seasonal influenza and 2009 influenza A (H1N1).[15,29-32] Although nine (50%) tested patients had positive culture results for bacteria and fungi in our reports, only one patient had fungal infection detected in normally sterile sites (pleural fluid and cerebrospinal fluid). It is possible that all patients received broad-spectrum antibiotics before admission or on admission. The effects of bacterial coinfections contributing to death may be limited in this case series.

Treatment with oseltamivir or zanamivir has been recommended for all patients with severe illness caused by 2009 influenza A (H1N1) infection.[33,34] Studies have shown that delayed antiviral treatment is associated with a high risk of progression to severe disease such as ICU admission, respiratory failure, prolonged hospital stay, and even death.[35,36] However, the observations in this report and two studies in China were unable to show the effects of antiviral therapy in reducing the severity of illness and mortality.[8,9] It is possible that most of our patients were admitted later (median time: 4–7 days), thus precluding timely antiviral treatment. The beneficial effects of corticosteroids and IVIG in severe cases of 2009 influenza A (H1N1) infection have not been established.[37] In this report, nonsurvivors were more likely than survivors to have received systemic corticosteroid and IVIG treatment, which may be reflected by the substantially more severe complications in non-survivors than survivors. Previous studies have showed that corticosteroid use was associated with a trend toward higher hospital mortality.[9] By contrast, a recent report demonstrated that low-to-moderate-dose corticosteroids might reduce mortality among patients with influenza A (H1N1) viral pneumonia and with PaO_2 /FiO_2 < 300 mmHg, patients with mild respiratory distress (PaO_2/FiO_2 ≥ 300 mmHg) did not benefit from corticosteroid therapy.[38] It is important to use corticosteroids with caution in the treatment of influenza infection.

Our study has several limitations. First, the current influenza surveillance system in China is mainly focused on patients with influenza-like illness symptoms, but national surveillance for influenza-associated pediatric mortality has not been implemented. We have no data of deaths from previous seasonal influenza infection to compare with this report. Second, the influenza vaccination status is uncertain for most patients in this case series, therefore, it is unknown whether influenza vaccination would have an effect on mortality owing to 2009 influenza A (H1N1) infection. Finally, this study is limited by its retrospective design, clinical evaluation and observations may have differed among hospitals or health care providers.

In conclusion, neutrophilia, lymphopenia and elevated CRP, as well as elevated LDH, CK, CK-MB, AST, and ALT may be risk factors for 2009 H1N1 influenza-associated pediatric death, and the most common causes of death are severe pneumonia, ARDS, and encephalopathy/encephalitis.

CONFLICT OF INTEREST

The authors have indicated they have no financial relationships relevant to this article to disclose.

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