original article

Features associated with severe disease in hospitalized children with 2009 influenza A (H1N1) infection at a university hospital in Riyadh, Saudi Arabia

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BACKGROUND AND OBJECTIVES: In 2009, pandemic H1N1 influenza A caused significant morbidity and mortality worldwide; however, available data on disease characteristics and outcome of hospitalized children is limited.

DESIGN AND SETTING: A prospective cohort study of children who required hospitalization because of the influenza A (H1N1) infection at King Khalid University Hospital in Riyadh, Saudi Arabia, over 6 months (July-December, 2009).

PATIENTS AND METHODS: Data was collected using a predesigned form for all admitted pediatric cases (0-12 years) presenting with the influenza-like illness and who tested positive for the novel influenza (H1N1) using reverse transcriptase polymerase chain reaction assay. The clinical course and features associated with the severe disease among such children were described

RESULTS: Out of 1103 children with the influenza-like illness, 375 (34%) were confirmed pediatric cases of influenza A (H1N1), of whom 50 (13.3%) required hospitalization. The median age was 3 years (range, 1 month-12 years). Fever was the most frequent symptom (94%) at admission, followed by cough (86%) and other symptoms including vomiting and diarrhea. The majority (70%) of children had at least one underlying medical condition, with bronchial asthma being the most common (40%). All cases were treated with oseltamivir. Five children (10%) were admitted to the ICU, 4 required mechanical ventilation, and 2 died (4%).

CONCLUSIONS: The majority of children with 2009 H1N1 influenza A–associated hospitalization in this series had an uncomplicated course. Respiratory complications and ICU admissions were more frequent in those with underlying disease, especially asthma and neuromuscular diseases. Efforts need to be focused prior to each influenza season and special emphasis needs to be given to children by immunizing them with H1N1 influenza A vaccination to avoid severe disease and minimize complications.

In the past century, pandemic influenza virus has circulated globally three times and caused increased morbidity and mortality among persons who have generally no risk factors for severe seasonal influenza.[1] In March and April 2009, cases of influenza-like illness (ILI) were first reported in Mexico, where it caused extensive disease among young adults,[2] and was associated with increased morbidity in the United States.[3] The outbreak was subsequently confirmed as pandemic influenza A (H1N1). The virus rapidly disseminated around the world. The first reports were quite alarming, describing severe complications and deaths among young, otherwise healthy people. Subsequently, a large array of clinical manifestations ranging from mild to severe illness were described.[4-6]

On June 3, 2009, the first case of pandemic influenza A (H1N1) virus was reported in Saudi Arabia.[7] As of 30 December 2009, a total of 15 850 laborato-

ry-confirmed cases had been reported by the Saudi Ministry of Health, with 124 deaths (case fatality rate of 0.8%).[8] The morbidity and mortality associated with seasonal influenza in the pediatric population have been well described.[9] However, the case series of 2009 pandemic influenza A (H1N1) virus infection reported a small number of children or did not present data on children separately.[8,10-12] In this report, we describe the clinical course and features associated with the severe disease in hospitalized children with 2009 influenza A (H1N1) at a university hospital in Riyadh, Saudi Arabia.

PATIENTS AND METHODS

Data were collected using a specially designed form for all patients presenting to the pediatric emergency department and outpatients clinics with ILI who tested positive for influenza A (H1N1) through reverse transcriptase polymerase chain reaction (RT-PCR) testing (Roche, Germany). The questionnaire included information about gender, age, nationality, history of recent travel, contact with a confirmed case of H1N1 or influenza, symptoms of influenza, vomiting, shortness of breath, headache, a decreased level of conscious, underlying medical conditions, radiologic and laboratory findings, antiviral/antibiotic use, need for admission to the intensive care unit (ICU), hospital course, and outcome.

Patients who presented with ILI (defined as oral temperature of more than 38°C) or a history of fever or chills and at least one influenza-like symptom were tested using nasopharyngeal aspirate. The diagnostic test used was the real-time RT-PCR assay that uses fluorogenic hydrolysis probe technology for detection of 2009 H1N1 influenza A virus. Potential subjects were identified through notification to the infection control department.

Only confirmed pediatric cases of 2009 H1N1 influenza infection that required hospitalization at King Khalid University Hospital (KKUH) during the period July-December 2009 were included in this analysis. KKUH is a major teaching hospital in Riyadh, Saudi Arabia, affiliated with King Saud University with a capacity of 920 beds, of which 110 are pediatric acute care beds and 9 are intensive care beds. The form was filled on admission by the infection control nurse and the course of hospitalization was followed by one of the authors by daily chart review. For descriptive statistics, SPSS for Windows version 17 (IBM Corp, Armonk, NY, USA) was used.

RESULTS

A total of 1103 children presented to the pediatric emergency department and outpatient clinic with influenza-like illness and had a swab sent for influenza A H1N1 PCR testing from July to December 2009. Of those, 375 (34%) were positive, of whom 50 (13.3%) required hospitalization. The median age at admission was 3 years, with a range of 1 month to 12 years. The highest percentage of cases was in the age group younger than 2 years, followed by those older than 5 years (**Table 1**). Males comprised 60% of the cases. The majority of cases (92%) acquired the infection inside Saudi Arabia. Six (12%) children had close contact with an index case of H1N1 in the family during the week prior to admission. The number of cases peaked on 8 August to 14 September, followed by a second peak from 24 October to 5 November 2009. Thirty-five (70%) children had 1 or more preexisting disorders. Bronchial asthma was the largest category (40%), followed by neuromuscular and chronic renal diseases.

Nosocomial transmission of 2009 H1N1 influenza

Table 1. Characteristics of children admitted with 2009 influenza A (H1N1).

Characteristics	Number (%)
Age (years), median	3
Age group (years)	
<2	19 (38)
2-5	14 (28)
>5	17 (34)
Sex: male	30 (60)
Preexisting condition[a]	
Any	35 (70)
Asthma	14 (40)
Neurologic disorder	7 (20)
Chronic renal disease	4 (11)
Diabetes mellitus	3 (8)
Genetic/Metabolic disorder	3 (8)
Hemoglobinopathy	3 (8)
Prematurity	1 (2)
Malnutrition	1 (2)
Admission to intensive care unit	5 (10)
Length of stay in hospital, days, median (IQR)[b]	5.2 (1-29)

[a]Children may have had more than one preexisting illness, [b]IQR: inter-quartile range.

was observed in one patient, a 2-year-old boy who had prune-belly syndrome with chronic renal disease, who subsequently died because of severe acute respiratory failure. The majority of patients presented more than 2 days after the onset of symptoms. Signs and symptoms on admission included fever (94%), cough (86%), shortness of breath (60%), running nose (38%), vomiting (28%), and diarrhea (18%) (**Table 2**). Influenza-related encephalopathy was suspected in a previously healthy 4-year-old girl because of a reduced level of consciousness; however, the cerebrospinal fluid (CSF) analysis and computed tomography scan of the brain yielded normal results. An 11-year-old boy who was a known diabetic patient presented with a picture of acute hepatitis (alanine aminotransferase 741 U/L, aspartate aminotransferase 1203 U/L), leucopenia, and mild sore throat, and was subsequently confirmed positive for pandemic H1N1. The workups for hepatitis viruses (A, B, C), cytomegalovirus, and Epstein-Barr virus were negative. Subsequently, he made a full recovery with normalization of liver enzymes 7 days after admission.

The mean white blood cell and platelet counts for the cohort included in this study were within normal limits on admission. One patient had leucopenia of 3000 cells/mm^3 that recovered within 3 days. Chest radiographs obtained on admission were reviewed by a pediatric pulmonologist, and the most frequent radiographic diagnosis was pneumonia in 13 (26%) patients. Lobar or segmental pneumonia was detected in 7 (14%) patients while interstitial pneumonia was detected in 6 (12%) patients. Two cases of pleural effusion were reported; however, in most of them, 33 (66%), chest radiographs were normal. The majority of hospitalizations were because of either respiratory distress or an underlying condition as a risk factor for the severe disease. Oseltamivir was administered to all patients for 5 or more days; and no adverse events were noted. The median length of stay was 5.2 days (interquartile range, 1-29 days). None of the cases had bacteremia; however, 7 patients were treated with antibiotics based on clinical and radiologic suspicion of bacterial superinfection. Five (10%) patients required admission to the ICU, all having at least one underlying medical condition, and 4 of them required mechanical ventilation including high-frequency oscillatory ventilation for 1 patient who developed acute respiratory distress syndrome. Two patients died because of respiratory failure with refractory hypoxemia (**Table 3**).

Table 2. Symptoms, and radiologic and laboratory findings of admitted pediatric influenza A (H1N1) cases.

Variables	Number (%)
Symptoms	
Fever	47 (94)
Cough	43 (86)
Shortness of breath	30 (60)
Running nose	19 (38)
Vomiting	14 (28)
Diarrhea	9 (18)
Lethargy	9 (18)
Chills	5 (10)
Radiologic findings	
Normal chest radiograph findings	33 (66)
Lobar or segmental consolidation	7 (14)
Interstitial pneumonia	6 (12)
Pleural effusion	2 (4)
Atelectasis	1 (2)
Consolidation	1 (2)
Laboratory findings, mean (SD) standard deviation (minimum-maximum)	
Leukocyte count ($\times 10^6$/mm^3)	9.9 (5.5) (3-25.1)
Hemoglobin (g/L)	114.5 (23.9) (10-172)
Platelets count ($\times 10^6$/mm^3)	279.2 (130.4) (60-668)

DISCUSSION

A few studies have been published concerning H1N1 influenza virus clinical manifestation and course in a pediatric setting.[13-16] Although limited, our case series documented the clinical features of H1N1 influenza virus infection in children hospitalized during the pandemic period of 2009. The majority of children in our series were under 2 years of age. This finding is congruent with the early Mexican epidemiologic studies that found children younger than 2 years to be most affected, with attack rates falling progressively with increasing age.[17] In contrast, the majority of the children in the initial series from the United States were between 5 and 14 years of age, though the rate of hospital admission was highest among children less than 5 years.[18] Children less than 5 years of age are considered to be at the highest risk for seasonal influenza-associated hospitalization.[19] Adults and elderly people, particularly those born before 1957 and likely exposed to previous influenza pandemics, seem to be more protected.[20] In our series, the clinical manifestations associated with the H1N1 influenza virus infection were similar to

Table 3. Characteristics and course of disease in children with 2009 influenza A (H1N1) who required admission to the intensive care unit.

Patient number	Age	Sex	Known comorbidity	Illness duration on admission	Complication	Duration of ICU stay	Outcome
1	3 months	F	Zellweger syndrome, seizure disorder	4 days	None	4 days	Recovered
2	2 years	M	Prune-belly syndrome, CRF, malabsorption	3 days	ARDS, DIC, ventilated for 2 wks, refractory hypoxemia	7 days	Died
3	3 years	M	Cerebral palsy	7 days	Pneumonia, ventilation for 3 wks	16 days	Recovered
4	8 years	M	Cerebral palsy, GERD	4 days	Pneumonia, ARDS, refractory shock	2 days	Died
5	12 years	F	Cerebral palsy, seizure disorder, bronchial asthma	2 days	Ventilated for 10 days	16 days	Recovered

F: Female, M: male, ADRS: acute respiratory distress syndrome, CRF: chronic renal failure, DIC: disseminated intravascular oagulation, GERD: gastroesophageal reflux disease, ICU: intensive care unit, wks: weeks..

those reported with seasonal influenza;[21] in particular, fever was constantly found.

Respiratory disturbances were the most common complications of infection, particularly virus related. We also found that approximately a third of cases presented with gastrointestinal manifestations (nausea, vomiting, and diarrhea), in addition to flu-like symptoms, which may indicate the more extensive viral replication.[22] A similar rate of gastrointestinal manifestations (28%) was reported from the United Kingdom.[14] The prevalence of underlying medical conditions (70%) was higher in our patients than those reported (37%-43%) in children hospitalized with seasonal influenza.[19,22] Diagnostic testing performed, as per the recommendation of Ministry of Health for patients with high-risk conditions throughout the pandemic, may have led to a greater number of confirmed cases and subsequent hospitalization than in previous influenza seasons. The high prevalence of asthma (40%) among children admitted with the H1N1 influenza virus infection was a prominent finding. Asthma has been identified as a significant risk factor for pandemic H1N1 influenza requiring hospital admission, and was reported in 21% to 30% in the larger series.[18] However, scarce pediatric data are available in the published studies, particularly regarding the severity of asthma or the clinical course and outcomes of children with asthma. Comparisons between pandemic H1N1 influenza and seasonal influenza in children with asthma are lacking, and most prior data on seasonal influenza did not present asthma separately from other chronic lung diseases. Asthma, or reactive airway disease, was listed as part of the underlying condition in only 3 of 36 children who died of pandemic H1N1 influenza; all of these children also had neurologic impairment.[5]

The reported frequency of neurologic complications following 2009 H1N1 influenza virus infection is unclear. The seasonal influenza-related encephalitis/encephalopathy had been reported from different countries. Neurological manifestations included mental status changes, behavior alterations, seizures, and focal neurologic deficits; 80% of such complications occurred among children less than 5 years of age, with outcomes ranging from complete resolution to severe neurologic sequelae.[23] Baltagi et al[24] described 4 cases of primary neurologic involvement by 2009 H1N1 influenza virus in children, all of which had abnormal electroencephalogram (EEG) and two had abnormal imaging studies. One patient in our series presented with reduced level of consciousness that improved within 36 hours of admission. EEG and brain magnetic resonance imaging are mandatory for the specific diagnosis of acute encephalitis; lumbar puncture is also required; however, influenza virus is rarely detected in CSF.[25]

The rates of pulmonary complications associated with the 2009 pandemic H1N1 influenza A infections appeared to be similar to those observed with seasonal influenza in previous pediatric studies. Thus, 10% of our patients required ICU care and 8% required mechanical ventilation, which is comparable with the reported rate of 15% and 8%, respectively, of children with seasonal influenza during three consecutive influenza seasons from 2001 to 2004.[19] Though 14% of our patients were suspected clinically and radiologically to have bacterial coinfection, the reported rate of confirmed bacterial coinfection was low, ranging from 1.3% to 1.6%.[10,26,27] Although it is unclear whether the previously reported association of bacterial coinfection with high mortality[19] is true for the 2009 H1N1 in-

fluenza, empirical antibiotic administration to children with influenza to possibly lower the risk of bacterial co-infection remains prudent, given the inability of currently existing laboratory or radiologic modalities to accurately differentiate bacterial from viral etiologies. Two children in our series died from infection because of both respiratory complication and refractory hypoxemia. Other reports have concluded that the H1N1 influenza virus infection in infancy and childhood has a low mortality rate.[13,14,16]

In the United States, about 540 laboratory-confirmed H1N1 pediatric deaths were reported among 8 million infected children aged between 0 and 17 years.[28] However, in Argentina, 13 deaths were recorded among 251 reported children (5%); 9 patients were found to have underlying chronic diseases, and none received timely antiviral treatment.[15] In the present series, oseltamivir was administered to all admitted children including 1 neonate, and no side effects were observed. A 5-day course of oral therapy seemed to be adequate, although a prolonged and high-dose treatment was necessary in children admitted to the ICU. Of note, the majority of the patients in our series had an uncomplicated course of the disease, and were discharged after a median length of hospital stay of 5 days. Some of the admissions may have been triggered by increased parental or physician worry, rather than solid medical indications, especially during the early weeks of the pandemic.

This study is limited by its single-center setting and lack of community epidemiologic data; the number of admitted children was small, thus limiting our ability to identify additional risk factors. The rate of bacterial superinfections could not be estimated accurately as we generally relied on culture results to detect this complication of influenza. Moreover, we did not study a comparable group of patients with seasonal influenza or other seasonal respiratory viral illness. The limited number of cases and short duration of our study preclude any definitive conclusions about how the present observed mortality compares with seasonal influenza-associated mortality.

In conclusion, our report probably provides the first description of children hospitalized during the 2009 pandemic influenza A H1N1 in Saudi Arabia. The majority had uncomplicated illness despite the frequent presence of high-risk conditions, especially bronchial asthma and neuromuscular diseases in our patient population. Additional studies elucidating the clinical and laboratory predictors of severity of illness, and comparing H1N1 with other strains seasonal influenza are required to optimize indications for the hospitalization of high-risk groups.

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