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Sunil Kumar BM, Satish Kumar KM, Rau ATK and Somashekhar AR

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ORIGINAL ARTICLE

Clinical profile of 'Pandemic Swine Flu (H1N1)' in children

Sunil Kumar BM[1], Satish Kumar KM[1], Rau ATK[1], Somashekhar AR[2]

ABSTRACT

Objective: The present study was undertaken to study the spectrum of pandemic pediatric H1N1 viral infection in children attending to tertiary care center in Bangalore.

Methods: Children who had an acute febrile respiratory illness were examined and suspected H1N1 infection cases were investigated with nasopharyngeal secretion swab and were managed according to guidelines for H1N1 infection. Patients found to be positive for H1N1-swine flu infection by RT-PCR were analyzed.

Results: A total of 282 pediatric patients with suspected H1N1 infection were clinically screened. 10.8 % patients had confirmed H1N1 virus infection. 56.7 % were male patients, more than 93% of the cases occurred above the age of one years. Only 6.6% of cases were seen below the age of one year. Clinically all of them had influenza like illness, more than 90% patients had cough and fever. 6.7% of the patients had epistaxis, 13.3% had erythematous maculopapular skin rashes and 43.3% patients had pneumonia. 20% of the patients went into shock, 16.7% developed ARDS and 20% of patients required mechanical ventilation. 13.3% patients succumbed to the illness.

Conclusion: The pediatric H1N1 infections presented initially with acute upper respiratory tract infection symptoms and signs. Children with H1N1 had high rate of complications and mortality. There were some atypical manifestations. There were no clinical features or laboratory findings which predicted worsening of illness. The timing of initiation of anti H1N1 drugs needs to be evaluated further to have maximum benefit from it.

Keywords: H1N1, pandemic, influenza, RT-PCR, Children, ARDS,MODS, Oseltamivir
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Introduction

The H1N1 influenza virus pandemic was one of the major health events during the end of this decade. It first caused infection in western coastal North America during March 2009 and caused a large outbreak in Mexico in April 2009, with subsequent cases all over the world [1,2,3]. Genetic characterization suggested that introduction of this virus into humans occurred as a single event, followed by multiple human to human transmission. On 11th of June 2009, WHO declared the outbreak a pandemic [4]. The clinical presentation of H1N1 infection varies from a usually mild influenza like illness to rapidly worsening pneumonia with ARDS [4,5]. Some countries have reported a greater number of severe illnessess and deaths; whereas others have reported only mild influenza like illness. Some studies have shown that one third of patients remain

Sunil Kumar BM[1], Satish Kumar KM[1], Rau ATK[1], Somashekhar AR[2]

[1]Department of pediatrics, M. S. Ramaiah Medical College, Bangalore, India
[2]Department of pediatrics and pediatric pulmonology, M. S. Ramaiah Medical College, Bangalore, India

Corresponding author: Sunil Kumar BM, MD

Department of pediatrics, M. S. Ramaiah Medical College, Bangalore- 560054, India
Phone No.: 09845172790
E-mail address: sunilminajagi@yahoo.com

asymptomatic, one third has a short febrile illness and one third require hospitalization [5].

India experienced a rapid increase in the number of H1N1 cases from mid May 2009 onwards and in response, screening, testing and management guidelines for H1N1 were initiated by the Government of India. We studied the clinical and epidemiological characteristics of pediatric H1N1 infections and describe the clinical spectrum, complications and outcome in our patients.

Methods

Patient population and setting:
We studied the clinical presentation, complications and outcome of H1N1 infected children attending to our referral hospital soon after our hospital was selected as a nodal treatment center for the pandemic. We studied the cases from 14th Aug 2009 to 28th Feb 2010 when the number of cases decreased.

Epidemiological investigations:
Children who had an acute febrile respiratory illness, defined as documented temperature > or = 37.8^{o} C of fever, with at least one of the following symptom or signs of cough, sore throat, nasal congestion or rhinorrhea were screened and examined. The patient's demographic data, presenting symptoms, significant medical history, vital signs, and examination findings were recorded, and relevant investigations were done on case to case basis. Their throat swabs were collected under existing guidelines and sent for analysis by RT-PCR. They were managed depending on severity of illness on either OP basis or as in patients as per Ministry of health and family welfare guidelines. Patients found to be positive for H1N1-swine flu infection by RT-PCR were analyzed.

Specimen collection
Nasopharyngeal swab samples were collected under strict precautions. H1N1-swine flu virus was confirmed in these specimens with the use of real time reverse-transcriptase- PCR assay at Neuro virology center NIMHANS Bangalore.

Statistical analysis*:*
Variable analysis was undertaken using Fisher's exact test (as appropriate) with SPSS software to identify features statistically associated with severe H1N1 infection. P value < 0.05 was considered as significant.

Results

A total of 282 pediatric patients with suspected H1N1 infection were clinically screened. 30 (10.8 %) patients had confirmed H1N1 virus infection by rRT-PCR testing and were analyzed. 18 others were found to be positive for seasonal flu. The results of the remaining 234 cases were either negative or unavailable for analysis as many of the swabs were not analyzed because of low priority group of patients. 56.7 % were male patients, more than 93% of the cases occurred above the age of one years. Only 6.6% of cases were seen below the age of one year (Table 1). Oseltamivir therapy was given in 80% of the cases.

Table 1. Age and sex distribution

Age group	Male	Females	Total (%)
< 1 year	1	1	2 (6.6)
1-5 years	5	5	10 (33.3)
6- 9 years	7	2	9 (30)
10-18 years	4	5	9 (30)
Total (%)	17 (56.7)	13 (43.3)	30 (100)

Clinical characteristics of H1N1virus infection

Cough was seen in all of the patients, fever was seen in 93% of the cases, 66.7% of them had pharyngitis, and 60% of them had rhinorrhea on examination. 30 % of them presented with breathlessness as one of the symptom (Table 2). Associated pre existing illness was seen in 33.3% of patients, 20% had altered sensorium at presentation and 13.3% had one or more episodes of clinical seizures in the course of illness.

6.7% of the patients had epistaxis as an associated complaint, 13.3% had erythematous maculopapular skin rashes and while 43.3% patients had chest X ray findings of pneumonia (Table 2). 20% of the patients went into shock, 16.7% developed ARDS and 20% of them required mechanical ventilation (Figure 1).

Table 2. Symptomatology of the 30 pediatric patients who had confirmed H1N1 infection.

Variables	Values (n, %)
Fever	28 (93.3)
Cough	30 (100)
Wheeze	8 (26.7)
Rhinorrea	18 (60)
Pharyngitis	20 (66.7)
Breathlessness	9 (30)
Myalgia	10 (33.3)
Vomiting	7 (23.3)
Diarrhea	4 (13.3)
Tachypnea	14 (46.7)
Hypotension	6 (20)
Seizure	4 (13.3)
Altered sensorium	6 (20)
Skin rash	4 (13.3)
Epistaxis	2 (6.7)
Pre existing disease	10 (33.3)
Leucocytopenia	8 (26.7)
Thrombocytopenia	5 (16.7)
Oseltamivir therapy	24 (80)

13.3% patients succumbed to their illness even though 100% of them had received oseltamivir. Altered sensorium, hypotension, ARDS and DIC were statistically (P value < 0.05) significant in patients with severe H1N1 infection and was associated with high mortality (Table 3-4).

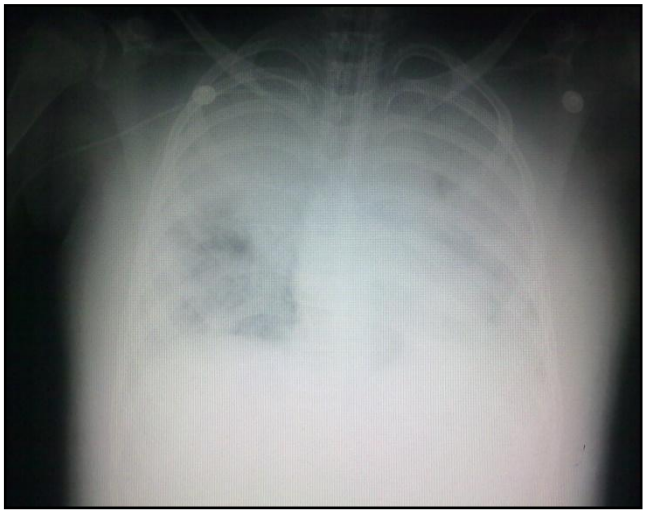

Figure 1. Chest X ray showing severe pneumonia with ARDS

Table 3. Complications seen in children positive for H1N1 infection.

Complications	Values (%)
Pneumonia	13 (43.3)
Mechanical ventilation	6 (20)
ARDS	5 (16.7)
Shock	5 (16.7)
DIC	5 (16.7)
Deaths	4 (13.3)

ARDS- Acute respiratory distress syndrome
DIC- Disseminated intra vascular coagulation

Discussion

During the peak of the pandemic many parents brought their children to hospital with minimal or no respiratory symptoms due to concern or for fear of H1N1 infection as little were known about the disease at that time. These patients were a part of the pandemic panic in the city and attended our tertiary care centre. However only a fraction of them tested positive for RT- PCR, while a majority of the tests

Table 4. Variable analysis of features potentially associated with severe H1N1 infection and high mortality by Fisher's Exact x2 test.

Variables	*P Value*
Altered sensorium	0.004*
Seizures	0.075
Skin rash	0.640
Hypotension	0.001*
Shock	0.001*
Pneumonia	0.026
ARDS	0.001*
DIC	0.001*
O2 requirement	0.018
Chest x rays	0.026
Oseltamivir treatment	0.338

ARDS- Acute respiratory distress syndrome
DIC- Disseminated intra vascular coagulation

were negative. A false negative test in patients who had infection with H1N1 virus would be more likely, if the patient had limited viral shedding or if the test were delayed. Some children had acute respiratory symptoms that did not fulfill the definition of Influenza like illness. It is unclear how many of these children had H1N1 infection.

In this pediatric H1N1 infection case series we observed that patients presented initially with acute upper respiratory tract infection symptoms and signs, majority of them were healthy before onset of the illness as was noted by Chudasama et al. [6]. 40.9% of them had involvement of lower respiratory tract. Several studies in animal models have demonstrated an increased ability of H1N1 virus, compared to seasonal flu strain to replicate in the lower respiratory tract and to cause pathogenic effects in lung tissues [7-10]. The H1N1 virus may also be preferentially affecting the lower respiratory tract as suggested by Ellen yeh, Robert F Luo et al [10]. Receptors have also been detected in the lungs to which H1N1 virus binds and causes primary viral pneumonia and ARDS with high case fatality rate [11]. The pathology of influenza is due directly to tissue damage, activation of inflammatory cascade. The symptoms are secondary to 'cytokine storm'. The pneumonia, pulmonary edema and ARDS are due to bronchiolar or alveolar viral cytopathology and cytokine storm. They are more prone to develop secondary bacterial pneumonia [12].

13.3% patients had died secondary to ARDS and refractory shock with MODS. There were no specific laboratory characteristics noted for severe illness even though 33.3% patients had an associated pre existing illness. There are suggested evidences that there is an association between severe H1N1 viral illness and immunoglobulin G2 (IgG2) subclass deficiency [13]. The role of immunoglobulin G2 (IgG2) subclass deficiency in pathogenesis of H1N1 infection requires to be explored further.

Rarely influenza causes neurological complications ranging from altered sensorium to brain death [14]. The pathogenetic mechanism is unknown. Neurological complications seen in our study was altered sensorium and seizures. The skin rashes seen in our cases were erythematous maculopapular. The pathogenic mechanism needs to be evaluated.

The risk factors for severe illness and deaths were not obvious, as they were seen predominantly in young, previously healthy children without any major risk factors. The more sick patients and case fatalities were showing pneumonia which rapidly worsened even with Oseltamivir treatment possibly suggesting direct injury to respiratory epithelium with a secondary cytokine storm. Contrary to other studies the contributing factors for deaths in our cases were neither delayed admission nor delayed initiation of Oseltamavir [6]. The exact timing of starting Oseltamivir needs to be evaluated as to have maximum beneficial effects on outcome.

Conclusion:

- The pediatric H1N1 infections presented initially with acute upper respiratory tract infection symptoms and signs. Majority of

H1N1 virus infection was mild influenza like illness.

- There were no any specific laboratory characteristics noted for severity of illness. Even though some severely ill patients had presented with lymphocytopenia and thrombocytopenia.
- The more sick patients and case fatalities were showing pneumonia which rapidly worsened even with oseltamivir treatment.
- Atypical manifestations seen in our cases were maculopapular skin rashes, epistaxis and normal total counts on hemogram. Most of the children were healthy before onset of the illness and were above the age of one year.
- Altered sensorium, hypotension, ARDS and DIC were significantly associated with severe H1N1 infection and was associated with high mortality.

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