CLINICAL PRESENTATION AND LUNG FUNCTION OF CHILDREN HOSPITALIZED WITH 2009 PANDEMIC INFLUENZA A (H1N1) PNEUMONIA

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Abstract. To determine the clinical presentation and subsequent lung function following pneumonia caused by 2009 pandemic influenza A (H1N1), pH1N1, in children aged 5-15 years hospitalized from June to September 2009, we contacted patients meeting the criterion 3-6 months post-hospitalization. Of the 88 patients contacted, 31 (35.2%) had pH1N1 and 57 (64.8%) had infections due to other viral pathogens (non-pH1N1), the mean age was 10.4 years and 52 (59%) were boys. Compared to non-pH1N1 patients, the pH1N1 patients were more likely to have a high fever (96.8% *vs* 77.2%, $p = 0.03$), sore throat (58.1% *vs* 33.3%, $p = 0.03$), and injected pharynx (80.6% *vs* 40.4%, $p = 0.001$). At 3-6 months after pneumonia onset, means for FVC, FEV_1, FEV_1/FVC, $FEF_{25-75\%}$, and PEF were within normal limit in both the pH1N1 and non-pH1N1 groups. Five (28%) of 18 pH1N1 children and 4 (20%) of 20 non-pH1N1 children had abnormal lung function results. All were restrictive type. In conclusion, pH1N1 pneumonia were more likely to present with high fever, sore throat, and pharyngeal injection than pneumonia from other viruses. About one quarter of the children who had pH1N1 had restrictive lung function 3-6 months after infection. This number did not differ from the non-pH1N1 group.

Keywords: pandemic H1N1, pneumonia, lung function, influenza

INTRODUCTION

The 2009 pandemic influenza A (H1N1), pH1N1, emerged in April 2009 in Mexico and spread rapidly worldwide. The clinical spectrum of pH1N1 infection varies from mild influenza like illness to pneumonia and acute respiratory distress syndrome (ARDS). Delayed antiviral therapy is a risk factor for poor outcomes (Jain *et al*, 2009; Chien *et al*, 2010; Lee *et al*, 2010). Recognizing the clinical characteristics of pH1N1 pneumonia is essential for early initiation of antiviral therapy. Several studies found high fever, cough, and rhinorrhea were the 3 most common clinical presentations of the pH1N1 infection in children (Hackett *et al*, 2009; Haura, 2010; Krittigamas, 2010; Libster *et al*, 2010).

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Pneumonia is a more severe presentation of pH1N1 infection and is not easily differentiated from pneumonia caused by other pathogens. Lung function subsequent to pneumonia caused by pH1N1 has not been well studied.

The aims of this study were to evaluate the clinical presentation and pulmonary function 3-6 months after pH1N1 pneumonia in hospitalized children, during the pH1N1 outbreak in Bangkok, Thailand, and to compare these with pneumonia caused by other viral pathogens occurring during the same period.

MATERIALS AND METHODS

Subjects

This study included children aged 5-15 years who were hospitalized with the diagnosis of pneumonia at the Department of Pediatrics, Faculty of Medicine Siriraj Hospital, between June and September 2009, and had respiratory specimens tested for respiratory viral pathogens. This was during the first pH1N1 outbreak in Bangkok. The medical records were retrospectively reviewed to collect demographic data, clinical features, and outcomes.

The parents of these children were contacted by telephone to invite them to join the pulmonary function study, which consisted of a one-time visit 3-6 months after their pneumonia. At the visit, respiratory symptoms were assessed and a physical examination was carried out. The height and weight were recorded and a pulmonary function test (PFT) was carried out. Written informed consent was obtained from parents and assent was obtained from children aged > 7 years. Patients whose parents could not be contracted, whose medical records could not be found or who were unable to perform the PFT were excluded.

This study was approved by the Siriraj Institutional Review Board.

Viral study

Patients who had pH1N1 virus detected by real-time reverse transcription-polymerase chain reaction (RT-PCR) from respiratory specimens were classified as having pH1N1. Those who were found to have other viral pathogens or in whom we were unable to identify a pathogen were classified as having non-pH1N1. The virologic tests routinely performed on the respiratory specimens in our center were real-time RT-PCR for seasonal influenza (A/H1, A/H3, and B) and pH1N1 viruses using the CDC protocol, an indirect immunofluorescent antibody (IFA) test using monoclonal antibodies to identify influenza A and B, respiratory syncytial virus (RSV), adenovirus and parainfluenza 1, 2, and 3. The specimens obtained routinely were nasopharyngeal washings.

Pulmonary function test

The SpirolabII MIR, Italy, was used to perform spirometry in the studied patients who had been free from respiratory tract infections for at least 2 weeks prior to the study. The PFT was done according to American Thoracic Society and European Respiratory Society guidelines (Pellegrino *et al*, 2005) by a trained respiratory technician. Pulmonary function parameters included forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), FEV_1/FVC, forced expiratory flow rate between 25-75% of vital capacity ($FEF_{25-75\%}$), and peak expiratory flow rate (PFR). The lung function results were expressed as percentages of predicted normal values. Those with a FVC < 80% of the predicted value were defined as having restrictive dysfunction and if FEV_1/FVC was <0.80 and the FEV_1 was <80% of predicted value, the patient was classified as

Table 1
Demographic data and presence of underlying diseases associated with severe pH1N1 infection.

	pH1N1 (*n*=31)	Non-pH1N1 (*n*=57)	*p*-value
Demographic data; mean ± SD			
Age (years)	10.3±3.4	10.4±3.0	0.89
Percent males	48%	65%	0.13
Weight (kg)	34.9±13.0	35.0±21.3	0.98
Height (cm)	136.4±20.2	135.5±18.5	0.83
Body mass index (BMI) (kg/m^2)	18.4±4.5	17.9±6.2	0.72
Underlying diseases associated with severe pH1N1 infection, *n* (%)	14 (45.2)	23 (40.4)	0.66
Asthma	4 (12.9)	3 (5.3)	0.24
Neuromuscular disease	3 (9.7)	2 (3.6)	0.34
Malignancy	2 (6.5)	9 (15.8)	0.32
Chronic renal disease	2 (6.5)	3 (5.3)	1.00
Congenital heart disease	1 (3.2)	4 (7.0)	0.65
Thalassemia	1 (3.2)	2 (3.6)	1.00
Immunodeficiency	1 (3.2)	0	0.35

having obstructive dysfunction (Mueller and Eigen, 1992; Pellegrino *et al*, 2005).

Statistical analysis

The data were expressed as mean ± SD or median (interquartile range, IQL) for normal or abnormal distribution data, respectively. Unpaired *t*-test or the Mann-Whitney *U* test where applied for quantitative data and the chi-square test for qualitative data were used to compare the data between the pH1N1 and non-pH1N1 groups. A *p*-value <0.05 was considered statistically significant. The data was analyzed with SPSS for Windows version 13.0.

RESULTS

Eighty-eight children, 52 (59.1%) boys, with a mean age of 10.4±3.1 years, who were hospitalized with pneumonia during the study period were included in the study. Thirty-one children (35.2%) had pH1N1 and 57 (64.8%) had non-pH1N1. In non-pH1N1 group, the viral etiologies identified were RSV (17.6%), seasonal influenza A (31.6%), and adenovirus (1.7%); in 49.1% no virus was identified.

The demographic data were not significantly different between the two groups (Table 1). Forty-five point two percent and 40.4% (*p*=0.66) of children in the pH1N1 and non-pH1N1 groups had pre-existing underlying diseases that correlated with a risk for severe pH1N1 infection (Table 1).

Clinical presentation

The most common symptoms of children with pH1N1 pneumonia were fever ≥37.8°C (96.8%), cough (93.5%), rhinorrhea (77.4%), and sore throat (58.1%) (Table 2). Compared to the non-pH1N1 group, children in the pH1N1 group were more likely to have fever ≥37.8°C, sore throat, and pharyngeal injection. The severity of pneumonia, as indicated by the respiratory

Table 2
Clinical presentation of children with pH1N1 and non-pH1N1 pneumonia.

	pH1N1 (*n*=31)	Non-pH1N1 (*n*=57)	Odd ratio (95% CI)	*p*-value
Clinical features, *n* (%)				
Fever ≥37.8°C	30 (96.8)	44 (77.2)	8.9 (1.1-71.4)	0.02[b]
Cough	29 (93.5)	49 (86.0)	2.4 (0.5-11.9)	0.48
Rhinorrhea	24 (77.4)	35 (61.4)	2.2 (0.8-5.8)	0.13
Sore throat	18 (58.1)	19 (33.3)	2.8 (1.1-6.8)	0.03[b]
Muscle pain	12 (38.7)	17 (29.8)	1.5 (0.6-3.7)	0.40
Dyspnea	11 (35.5)	19 (33.3)	1.1 (0.4-2.8)	0.84
Headache	10 (22.3)	18 (31.6)	1.0 (0.4-2.6)	0.95
Nausea-vomiting	9 (29.0)	16 (28.1)	1.0 (0.4-2.7)	0.92
Diarrhea	3 (9.7)	5 (8.8)	1.1 (0.2-5.0)	1.00
Joint pain	2 (6.5)	2 (3.5)	1.9 (0.3-14.2)	0.61
Physical findings, *n* (%)				
Temperature (°C)[a]	38.7 ± 0.7	38.4 ± 1.1	-	0.08
RR (/min)[a]	29.1 ± 6.9	29.4 ± 9.1	-	0.88
PR (/min)[a]	116.3 ± 20.4	117.0 ± 18.8	-	0.88
SpO_2 (%)[a]	96.0 ± 5.2	96.6 ± 3.3	-	0.55
Injected pharynx	25 (80.6)	23 (40.4)	6.2 (2.2-17.4)	0.001[b]
Injected tympanic membrane	2 (6.5)	1 (1.8)	3.9 (0.3-44.4)	0.28
Chest retraction	12 (38.7)	15 (26.3)	1.8 (0.7-4.5)	0.23

[a]Mean ± SD; [b]Significant

rate and oxygen saturation on admission, was comparable between the 2 groups (Table 2).

The length of hospital stay in the non-pH1N1 group was longer than in the pH1N1 group [median (IQR) 6 (3-13) *vs* 4 (3-6) days, respectively, $p = 0.03$]. The percent of patients admitted to the ICU were not significantly different (3.2% of the pH1N1 and 7% of the non-pH1N1 group, $p = 0.65$) and none of the patients in either group required mechanical ventilation or died.

Pulmonary function testing 3-6 months post-hospitalization

Eighteen and 20 children in the pH1N1 and non-pH1N1 groups, respectively, returned for the PFT 3-6 months after hospitalization. The basic characteristics of the 2 groups were not significantly different from each other (Table 3). All the children were well and had a normal physical examination on the day of the PFT.

In the pH1N1 group, restrictive pulmonary dysfunction was found in 5 children (28%) 4 were mild and 1 was moderate in severity. Of the 20 children in the non-pH1N1 group tested, 4 (20%) had restrictive dysfunction, 3 mild and 1 moderate. There were no obstructive defects in either group. There were no significant differences between the 2 groups in lung function (pH1N1= 28%, non-pH1N1 = 20%, $p = 0.71$).

The means of all the pulmonary function parameters (FVC, FEV_1, FEV_1/FVC,

Table 3
Basic characteristics of children who underwent pulmonary function testing.

	pH1N1 (*n*=18) (mean ± SD)	Non-pH1N1 (*n*=20) (mean ± SD)	*p*-value
Age (years)	10.1 ± 3.8	11.8 ± 3.3	0.15
Percent males	72%	50%	0.16
Weight (kg)	37.4 ± 15.4	47.9 ± 30.3	0.27
Height (cm)	137.6 ± 22.2	145.6 ± 22.0	0.18
BMI (kg/m^2)	19.1 ± 3.1	20.8 ± 8.0	0.37
Duration between pneumonia onset and PFT (months)	5.1 ± 1.6	5.5 ± 1.2	0.46

Table 4
Pulmonary function testing in children with pH1N1 and non-pH1N1 pneumonia.

PFT (%predicted value)	pH1N1 (*n*=18) (mean ± SD)	Non-pH1N1 (*n*=20) (mean ± SD)	*p*-value
FVC	84 ± 11.1	88 ± 16.6	0.33
FEV_1	89 ± 12.4	92 ± 14.2	0.47
FEV_1/FVC	94 ± 4.5	93 ± 4.2	0.47
PEF	104 ± 31.2	90 ± 18.4	0.11
$FEF_{25-75\%}$	104 ± 26.1	101 ± 19.1	0.76

PEF and $FEF_{25-75\%}$) in the pH1N1 and non-pH1N1 groups were greater than 80% of the predictive values and no statistically significant differences were seen between the two groups (Table 4).

DISCUSSION

The common presentating symptoms of children with pH1N1 hospitalized for pneumonia in this study were fever, cough, rhinorrhea, and sore-throat. These results are similar to other studies (Hackett *et al*, 2009; Haura *et al*, 2010; Krittigamas *et al*, 2010; Libster *et al*, 2010). Diarrhea was found in 9.7% in our study, much lower than the 20% reported in other studies (Hackett *et al*, 2009; Haura *et al*, 2010; Krittigamas *et al*, 2010).

Compared to the non-pH1N1 group, fever, sore throat, and pharyngeal injection were more common in pH1N1 group. Gordon *et al* (2010) compared the clinical features between those with H1N1 influenza and seasonal influenza A and found sore throat, nausea, and loss of appetite were the differences in clinical presentation. Although these symptoms are non-specific, they may help clinicians decide on specific antiviral therapy, which may affect outcomes.

The results of pulmonary function testing following pneumonia are affected by various factors, such as the causative pathogen, age of the patient and the time of the study. There are few reports of pulmonary function in children following

pneumonia, and no studies after pH1N1 2009 pneumonia have been reported. Most reports are following RSV pneumonia or lower respiratory tract infections (LRTI). Studies during infancy demonstrate increased airway resistance (Stokes *et al*, 1981; Dezateux *et al*, 1997; Broughton *et al*, 2007). Airway obstruction and airway hyperresponsiveness after RSV LRTI may still be detected in school age children and adolescents (Hall *et al*, 1984; Sly and Hibbert, 1989; Lerdluedeeporn *et al*, 1999; Stein *et al*, 1999; Hyvarinen *et al*, 2007). A report of pulmonary function among 38 children with SARS found a median age of 13.6 years, and showed 2 children had mild obstructive airway disease and 2 had mild restrictive airway disease 6 months after diagnosis (Li *et al*, 2004). Teper *et al* (1999) evaluated pulmonary function on an average of 9.3 months (3 to 14 months) after a severe adenoviral LRTI in young children with a mean age of 1.32 years and found airway obstruction and diminished pulmonary compliance not responsive to bronchodilators. Another study in children after adenovirus pneumonia among children at a mean age of 3.2 years showed 65% had evidence of airway obstruction at a mean age of 16.1 years (Sly *et al*, 1984).

The results of this study suggested pH1N1 did not contribute to more severe respiratory damage or sequelae than any other respiratory pathogens. About one quarter of patients had abnormal pulmonary function at 3-6 months after illness, but most of the abnormalities were mild restrictive type. The average pulmonary function parameters of FVC, FEV_1, FEV_1/FVC, PEF and $FEF_{25-75\%}$ in both groups, were greater than 80% of the predicted values. No obstructive dysfunction was found even though asthmatic children were included in the study. This is probably due to the fact asthma in our children was well controlled. The longer term effect pulmonary function in this cohort should be further studied.

The limitations of this study were the data were collected retrospectively, which may limit the accuracy and availability of some information. The number of patients that returned for the PFT was small and there were no PFT results at discharge to compare to. In spite of these limitations, the results of this study suggested pH1N1 did not affect pulmonary function any more than the other viral pathogens.

In conclusion, pneumonia caused by pH1N1 in children presented with fever, sore throat, and pharyngeal injection more frequent than the other pathogens. However, pH1N1 did not cause a more severe clinical course or have a worse consequence to pulmonary function. Approximately a quarter of the patients in both groups had abnormal pulmonary function, a restrictive pattern and most were mild.

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