Pandemic Influenza (H1N1) 2009 of Pediatric Patients at Thammasat University Hospital

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Background: *An emerge of pandemic influenza H1N1 2009 has devastated the global community. Pediatric population is among the groups with high attack rate.*
Objective: *To study the clinical presentation of pediatric patients (0-15 years old) infected with influenza H1N1 2009 and to evaluate the sensitivity and specificity of the rapid influenza test.*
Material and Method: *Retrospective data was collected from the medical reports of patients presenting with influenza like illness (ILI) whose samples from nasal swab were tested for H1N1 using reverse transcription polymerase chain reaction (RT-PCR) during June-September 2009 at the Thammasat University Hospital.*
Results: *Of 68 patients, 26 were confirmed to have H1N1 2009 strain. Of these, 61.5% were older than 5 years old; 26.9% had underlying conditions and 38.4% had hospitalization. All 26 patients presented with fever and cough; 73% had coryza; 57.6% had sore throat; and 88.4% had injected throat. Six patients (23%) had pneumonia. Patients younger than 5 years old experienced dyspnea and had abnormal results of a chest radiograph significantly more often than patients older than 5. Patients with H1N1 2009 strain were more likely to have sore throat, myalgia, and injected throat than non H1N1 2009 group. However, chest wall retraction and abnormal chest radiograph were found significantly less often in the H1N1 group compared to the non-H1N1. No death case was reported.*

The rapid influenza test was found to have sensitivity of 80%, specificity of 64%, positive predictive value of 74.5%, and negative predictive value of 84.3% when compared to RT-PCR method.
Conclusion: *During pandemic period, older children with influenza like illness had novel H1N1 2009 infection more than younger children. The majority of pediatric patients presented with mild symptoms. Patients aged below 5 years more frequently experienced pneumonia. The rapid influenza test showed a high sensitivity but low specificity.*

Keywords: *Pandemic H1N1 2009, Influenza, Pediatric*

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The pandemic of influenza in 2009 was an outbreak of a novel strain of H1N1 influenza virus, which contains genes from viral strains isolated from human, swine and birds[1]. Without preexisting immunity, people throughout the world could easily be infected. The outbreak began in Mexico and quickly spread through the global community[2-4]. In June 2009, the World Health Organization declared the outbreak a pandemic with the highest level of 6 on the epidemic scale. Though WHO announced the end of the pandemic in August 2010, this does not mean that the H1N1 virus has gone away[5]. Based on experience with past pandemics, the authors' expect the H1N1 virus to take on the behavior of a seasonal influenza virus and continue to circulate for some years to come.

It has been reported that the clinical manifestations of 2009 pandemic flu differ from those of seasonal flu[6]. Severe symptoms can be found in young and healthy population. People with underlying conditions as well as pregnant women are the risk group; however, factors contributing to increase the severity of the disease are not well defined.

In the present study, the authors evaluated the clinical presentation of patients, age 0-15 years, who were infected with H1N1 2009 strain. The authors also evaluated the reliability of the rapid influenza test compared to the reverse transcription polymerase chain reaction (RT-PCR) method.

Material and Method

Study population and design

Retrospective analysis of clinical data obtained from patients' medical records was conducted. An inclusion criterion was individual presented with an influenza-like illness (ILI) who had nasal swab study

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for H1N1 2009 using RT-PCR technique. Study subjects consisted of pediatric patients between 0-15 years of age who visited Thammasat University Hospital between June and September 2009. Clinical profiles including age, gender, underlying conditions, clinical manifestations, and laboratory test *i.e.* Rapid influenza test (SD Bioline Influenza Antigen A/B) and chest radiograph were also statistically assessed.

Patients with ILI were defined[2] as patients who presented with fever more than 38°C, having cough or sore throat, and/or having coryza, malaise, nausea, vomit and diarrhea.

Statistical analysis

The clinical characteristics of the present study population were summarized with descriptive statistics. Comparison of patients with H1N1 2009 strain infection and ILI patients infected with non-H1N1 2009 strains was assessed using unpaired t-tests for continuous data and Chi-square tests for dichotomous data, with both reported as p-values. Statistical measures of the performance of the rapid influenza test were also assessed compared with the confirmation test (RT-PCR).

Results

At Thammasat University Hospital during June-September 2009, a total of 72 patients presented with ILI and received the confirmation diagnosis using RT-PCR. Of these, medical records of 68 patients could be obtained. Patients were from 3 months old to 14 years old (mean 6 years); 39 male (57.4%) and 29 female (42.6%). 26 from 68 patients (38.2%) were infected with

Table 1. Demographic, clinical and laboratory data of influenza like illness patients with pandemic (H1N1) 2009 compared with non pandemic (H1N1) 2009

Patient Characteristic	Pandemic (H1N1) 2009 n = 26	Non Pandemic (H1N1) 2009 n = 42	p-value
Male-no (%)	15 (57.6)	24 (57.1)	1
Age-year			
Mean	7.9 $\pm$ 4.5	4.8 $\pm$ 4.6	0.03
Age-no (%)			
< 5 years	10 (38.4)	30 (71.4)	0.24
$\geq$ 5 years	16 (61.6)	12 (28.6)	0.11
Underlying diseases-no (%)	7 (26.9)	8 (19)	0.58
Symptom-no (%)			
Fever	26 (100)	42 (100)	1
Cough	26 (100)	39 (85.7)	0.281
Sore throat	15 (57.6)	9 (21.4)	0.004
Injected conjunctiva	1 (3.8)	1 (2.3)	1
Headache	7 (26.9)	5 (11.9)	0.189
Rhinorhea	19 (73)	28 (66.6)	0.788
Nausea	6 (23)	15 (35.7)	0.297
Vomiting	2 (7.6)	10 (23.8)	0.112
Dyspnea	6 (23)	12 (28.5)	0.779
Diarrhea	1 (3.8)	5 (11.9)	0.395
Myalgia	6 (23)	2 (4.6)	0.047
Sign-no (%)			
Injected throat	23 (88.4)	27 (64.2)	0.046
Chest wall retraction	1 (3.8)	11 (26.1)	0.022
Abnormal lung signs	10 (38.4)	20 (47.6)	0.165
Abnormal CXR-no (%)	6 (23)	23 (54)	0.013
Hemoglobin-gm%			
Median (Range)	12 (11-13)	12 (10-15)	1
Leukocyte count-per mm^3			
Median (Range)	7,000 (3,300-15,400)	8,790 (2,800-17,300)	0.315
Platelet count-per mm^3			
Median (Range)	251,500 (159,000-420,000)	267,000 (44,000-473,000)	0.451

the H1N1 2009 strain, confirmed by the RT-PCR method.

Table 1 shows demographic data and clinical data of patients with H1N1 2009 strain (RT-PCR positive) compared with patients with non-H1N1 2009 strains (RT-PCR negative). Among the RT-PCR-positive group, patient's age ranged from 10 months-14.7 years (mean 7.9 years). Of 26 patients, 7 (26.9%) patients had an underlying disease: 2, asthma; 3, allergic rhinitis; 1, congenital heart disease; and 1 GERD. All patients had fever and cough (Table 1). Sore throat, myalgia and injected throat were significantly found in H1N1 2009 group whereas difficulty breathing which requires accessory muscles and abnormal chest radiograph were more frequently found in the non-H1N1 2009 group (Table 1).

All abnormal chest radiograph results found in the H1N1 2009 group (6 cases) showed an interstitial infiltration pattern while the non-H1N1 2009 group (23 cases) showed various patterns including the interstitial infiltration (18 cases), alveolar infiltration (3 cases) and atelectasis (2 cases).

The complete blood count (CBC) study revealed that there was a non-significant difference between median white blood cells of the two groups: 7,000 cells/mm^3 in the H1N1 2009 infected group, 8,790 cells/mm^3 in the non-H1N1 2009 group.

Among patients infected with the H1N1 2009 strain, the clinical outcomes were compared between patients under 5 years of age and patients 5 years and over (Table 2). It is noteworthy that symptoms such as dyspnea and finding of abnormal chest radiograph appeared significantly more common in the younger group (Table 2).

Of 68 patients who received the confirmation diagnosis test (RT-PCR), 59 were tested with the screening method, the rapid influenza test (Table 3).

Table 2. Clinical features of Pandemic (H1N1) 2009 patients by age group

Clinical features	Age < 5 year (n = 10) No. (%)	Age ≥ 5 year (n = 16) No. (%)	p-value
Symptom			
Fever	10 (100)	16 (100)	1
Cough	10 (100)	16 (100)	1
Sore throat	4 (40)	11 (68.7)	0.228
Injected conjunctiva	0 (0)	1 (6.2)	1
Headache	2 (20)	5 (31.3)	0.668
Rhinorhea	7 (70)	12 (75)	1
Nausea	2 (20)	4 (25)	1
Vomiting	1 (10)	1 (6.25)	1
Dyspnea	5 (50)	1 (6.25)	0.018
Diarrhea	1 (10)	0 (0)	0.385
Myalgia	2 (20)	4 (25)	1
Sign			
Injected throat	9 (90)	14 (87.5)	1
Chest wall retraction	1 (10)	0 (0)	0.385
Abnormal lung signs	6 (60)	4 (25)	0.109
Abnormal CXR	5 (50)	1 (6.2)	0.018

Table 3. Sensitivity and specificity of rapid influenza test A/B compared to RT–PCR

Rapid test for Influenza	RT-PCR Influenza H1N1		Total
	Positive	Negative	
Positive	20	7	27
Negative	5	27	32
Total	25	34	59

The rapid influenza test has the sensitivity 80%, specificity 64%, positive predictive value of 74.5% and negative predictive value of 84.3% when compared to RT-PCR method.

From the twenty-six H1N1-2009 infected patients, 12 patients received oseltamivir (oseltamivir group) and 14 patients did not received oseltamivir (non oseltamivir group). The patients in oseltamivir group experienced defervescence within 1-3 days (mean 1.92 days) whereas non oseltamivir group experienced defervescence within 1-4 days (mean 2.2 days) ($p = 0.382$). However before treatment, half of patients in oseltamivir group had initial abnormal chest radiograph but no patient in non oseltamivir group had this finding.

Ten (38.4%) of the total 26 patients with H1N1 2009 strain had to be taken care in the hospital. 30% of these had an underlying condition while 25% of 16 patients with H1N1 2009 strain, who did not require in-patient care, had an underlying condition.

Discussion

In the present study over the 3-month period of the H1N1 2009 pandemic, the authors found more cases among children aged 5-15 years than among children below 5. This is consistent with other reports[7,8]. The average age of the confirmed cases is 7.9 years old which is higher than that of the previous report by Ginocchio (2.5 years old)[9]. This may be discussed that the previous report was conducted in hospitalized patients which had tendency to be younger than our patient group[10,11]. In the present study, the authors found that the clinical outcomes were more severe in the younger children than in the older age group. Dyspnea, using accessory muscles to help breathing and abnormal chest radiograph were present more frequently in the young children. Symptoms such as headache, sore throat which were found more often in the older children may be because these symptoms are difficult to evaluate in the young patients. However this finding is not significant statistically.

It was found that the symptoms including sore throat and myalgia were more prevalence in the H1N1 2009 cases. This finding is consistent with other studies which reported the higher prevalence of sore throat, lower respiratory tract symptoms, and gastrointestinal tract symptoms among patients with a novel H1N1[4,12]. Although in the real situation, the authors cannot use these symptoms to differentiate between cases with pandemic flu and seasonal flu[13]. However, the findings of the present study are limited primarily by the design of retrospective medical record review.

In the present study, the authors found that non H1N1 2009 had more dyspnea and abnormal chest radiograph than patients with pandemic flu. This may be because the patients with critically ill were more likely to get the RT-PCR test. It was found that the majority of the abnormal chest radiograph was from the secondary bacterial infection.

The authors found that all abnormal chest radiographs result in the H1N1 2009 group showed an interstitial infiltration pattern. This is in contrast to a report by Larcombe et al in which the consolidation pattern was more common[14]. It may be due to the fact that the present study by Larcombe focused mainly on severely ill inpatients.

The gold standard methodology for diagnosis of influenza is viral culture which is troublesome and mainly done in the research laboratory. The detection of viral RNA such as using RT-PCR has high sensitivity and specificity and is thus used as a confirmation test. However this test is expensive, time consuming and is still done in tertiary health centers. The rapid influenza test which detects antigens of both Influenza A and B virus is therefore used more often. Nevertheless, this method cannot differentiate the true cause. When tested in seasonal flu, the specificity value of more than 90% and the sensitivity value of 20-70% were observed in this rapid influenza test[15-17]. In the present study, we found a sensitivity value of 80% and specificity value of 64% when used in the pandemic influenza patients. These values were higher than other previous reports[18-21]. Factors such as tested sample, sample collection and transportation techniques and patient's age were reported to contribute to the sensitivity of the testing method while the specificity may depend on the situation of each epidemic[22,23]. It is important to develop a more reliable rapid test to aid the diagnosis of this disease.

The present study showed no difference of outcomes between patients who received oseltamivir and who did not. However, the oseltamivir group had more severity of initial symptoms than the non oseltamivir group. Generally, mild or uncomplicated influenza cases can be ameliorated without the need of antiviral agents. Several studies have showed that antiviral agents, if administered in the early course of disease, have reduced the severity as well as mortality[24,25]. Antiviral treatment is recommended for severe, complicated, or progressive illness patients, patients with underlying conditions such as asthma, DM, renal dysfunction, obesity, as well as

immunocompromised patients, and pregnant women. Patients under 2 or older than 65 years of age should also be treated promptly[26]. Treatment is most effective when started in the first 48 hours of illness[27].

Conclusion

During pandemic period, older children with influenza like illness had novel H1N1 2009 infection more than younger children. The majority of pediatric patients presented with mild symptoms. Patients aged below 5 years more frequently experienced pneumonia. The rapid influenza test showed a high sensitivity but low specificity.

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Potential conflicts of interest

None.

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วัตถุประสงค์: *เพื่อศึกษาอาการทางคลินิกของผู้ป่วยเด็กอายุ 0 – 15 ปี ที่ติดเชื้อไข้หวัดใหญ่ระบาดใหญ่ (เอ็ช1เอ็น1) 2009 และศึกษาความไวความจำเพาะของการตรวจวินิจฉัยไข้หวัดใหญ่ระบาดใหญ่ (เอ็ช1เอ็น1) 2009 ด้วยวิธี rapid influenza test*

วัสดุและวิธีการ: *ศึกษาแบบย้อนหลังโดยรวบรวมข้อมูลจากเวชระเบียนผู้ป่วยเด็ก ที่มาด้วยอาการคล้ายไข้หวัดใหญ่ (Influenza like illness, ILI) และได้รับการทำ nasal swab เพื่อตรวจหาไข้หวัดใหญ่ระบาดใหญ่ (เอ็ช1เอ็น1) 2009 ด้วยวิธี transcription polymerase chain reaction (RT-PCR) ในโรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติ ช่วงเดือนมิถุนายน พ.ศ. 2552 ถึงเดือนกันยายน พ.ศ. 2552*

ผลการศึกษา: *จากการศึกษาผู้ป่วยเด็กที่มาด้วยอาการคล้ายไข้หวัดใหญ่ จำนวน 68 ราย พบเป็นไข้หวัดใหญ่ระบาดใหญ่ (เอ็ช1เอ็น1) 2009 จากการตรวจ RT-PCR จำนวน 26 ราย โดยเป็นผู้ป่วยที่อายุน้อยกว่า 5 ปี และมากกว่าหรือเท่ากับ 5 ปี ร้อยละ 38.5 และ 61.5 ตามลำดับ ผู้ป่วยร้อยละ 26.9 มีโรคประจำตัว ร้อยละ 38.4 เข้ารับการรักษาแบบผู้ป่วยใน โดยพบอาการไข้และไอทุกราย (ร้อยละ 100) ส่วนใหญ่มีอาการน้ำมูก (ร้อยละ 73) เจ็บคอ (ร้อยละ 57.6) และตรวจพบคอแดง (ร้อยละ 88.4) จากการศึกษาผู้ป่วยไข้หวัดใหญ่ระบาดใหญ่ (เอ็ช1เอ็น1) 2009 มีปอดอักเสบ 6 ราย คิดเป็นร้อยละ 23.1 ไม่มีรายใดเสียชีวิต ผู้ป่วยที่มีอายุน้อยกว่า 5 ปี พบมีอาการหายใจหอบ และภาพรังสีทรวงอกผิดปกติมากกว่าผู้ป่วยที่มีอายุมากกว่าหรือเท่ากับ 5 ปีอย่างมีนัยสำคัญทางสถิติ ผู้ป่วยไข้หวัดใหญ่ระบาดใหญ่ (เอ็ช1เอ็น1) 2009 มีอาการเจ็บคอ ปวดกล้ามเนื้อ และตรวจพบคอแดงมากกว่า แต่ตรวจพบใช้กล้ามเนื้อช่วยหายใจและภาพรังสีทรวงอกผิดปกติน้อยกว่าผู้ป่วยที่ไม่ใช่ไข้หวัดใหญ่ระบาดใหญ่ (เอ็ช1เอ็น1) 2009 อย่างมีนัยสำคัญทางสถิติ การตรวจวินิจฉัยไข้หวัดใหญ่ระบาดใหญ่ (เอ็ช1เอ็น1) 2009 โดยการทำ rapid influenza test พบว่ามีความไวเท่ากับร้อยละ 80 ความจำเพาะเท่ากับร้อยละ 64 ค่าพยากรณ์บวกเท่ากับร้อยละ 74.5 ส่วนค่าพยากรณ์ลบเท่ากับร้อยละ 84.3*

สรุป: *ในช่วงที่มีการระบาดของไข้หวัดใหญ่ (เอ็ช1เอ็น1) 2009 ผู้ป่วยเด็กที่มาด้วยอาการคล้ายไข้หวัดใหญ่ตรวจพบเป็นไข้หวัดใหญ่ระบาดใหญ่ (เอ็ช1เอ็น1) 2009 ในเด็กโตมากกว่าเด็กเล็ก ผู้ป่วยเด็กส่วนใหญ่มีอาการไม่รุนแรง เด็กเล็กพบมีอาการปอดอักเสบมากกว่าเด็กโต การตรวจวินิจฉัยโดยชุดทดสอบ rapid influenza test มีความไวสูงแต่มีความจำเพาะต่ำ*