The Clinical Features and Fever Related Factors of Hospitalized Pediatric Patients with Novel Influenza A (H1N1) Virus in a Regional Hospital in Middle Taiwan

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Abstract

Background: Since the Communicable Disease Center reported the first aboratory-confirmed case of novel H1N1 in June 2009, there has been a nation-wide pandemic of influenza A (H1N1) virus infection in Taiwan. In this paper we describe the clinical characteristics of non-severe novel H1N1-infected pediatric patients and analyze factors related to the course of their illnesses.

Patients and methods: Between August 19 and December 28, 2009, we admitted 109 non-severe novel H1N1-infected pediatric patients confirmed by the Influenza (A+B) Antigen test. By reviewing medical charts, we collected data from the onset of illness until afebrile status for these 109 pediatric inpatients was achieved.

Results: Of the 109 patients, 15% had a highest forehead temperature less than 38.0°C. Eighty four percent of the patients had less than 25% lymphocytes and 95% had over 6% monocytes. Ninety percent had less than 3% eosinophils. Seventeen percent received a Mycoplasma antibody test and in 61% of these it was higher than normal. Seventy three percent had an abnormal chest x-ray. All patients were treated with oseltamivir; 97% within the first 3 days after onset of fever. The average duration of fever was 4.37 days if oseltamivir was given on the first day of fever, 5.22 days if given on the second day, and 6.06 days if given on and after the third day. Thirty five percent were treated with antibiotics, but the duration of fever of treated patients was significantly longer than that of untreated patients. The highest forehead temperature was the only factor significantly associated with the duration of fever after oseltamivir treatment.

Conclusions: Most non-severe novel H1N1-infected pediatric patients presented with lymphocytopenia, eosinopenia, monocytosis, and abnormal chest x-ray findings. Fever less than 38°C could not be a deciding factor in screening for novel H1N1. Whether or not patients were treated with antibiotics, the earlier oseltamivir was administered, the shorter was the duration of fever during the illness.

Key words : Influenza A, H1N1, Oseltamivir

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1.Introduction

Influenza A virus is known to be a cause of epidemics annually and occasional pandemics. In late March 2009, Mexican health authorities announced an outbreak of a novel H1N1 swine influenza virus[1]. In April 2009, the Centers for Disease Control and Prevention (CDC) confirmed the first two cases of human infection with a pandemic influenza A (H1N1) virus in the United States[2].The pandemic influenza A (H1N1) virus has subsequently caused a global outbreak

of febrile respiratory infection ranging from self-limited to severe illness[3].

The Centers for Disease Control, R.O.C. (Taiwan) reported the first laboratory-confirmed novel H1N1 case in June 2009[4].4 In order to share our experience of caring for non-severe novel H1N1 cases, we reviewed those patient's medical charts and collected data regarding their clinical features from the onset of disease afebrile status.

The duration of fever is not only the most important symptom to patient's families, it is also the focus of treatment by pediatricians, but not so many papers have discussed it in detail. In this article, we focused on the courses of fever of those patients and also tried to find factors associated with a shorter time to defervescence.

2.Materials and Methods

2.1 Study Population

From August 19, 2009 to December 18, 2009, 109 pediatric patients were hospitalized with an influenza-like illness. All were tested positive for influenza A by nasal or throat swabs with the use of Influenza (A+B) Antigen test (Espline Influenza A&B-N, Fujirebio, Japan), which could detect influenza A and influenza B infection.

Influenza (A+B) Antigen test was performed on patients with a forehead temperature of 38℃ or higher. Patients with a body temperature less than 38℃ but presented with influenza-like illness or had a contact history with novel H1N1-infected patients (family members or classmates) were also tested for H1N1.

2.2 Data collection

We used retrospective medical charts to collect demographic data, clinical features, laboratory test results, chest X-ray findings, treatment received, and the course of fever.

Cases were divided into 3 age groups: ≦ 6 years old, 7-12 years old, and 13-18 years old. The body mass index (weight in kilograms divided by the square of the height in meters) was calculated, and cases were divided into four groups based on BMI (underweight, normal, overweight, and obese) according to the Child and Adolescent Obese Criteria defined by Taiwan's Department of Health[5].

Mycoplasma pneumoniae infection was diagnosed based of the result of the Serodia Myco II Microtiter Particle Agglutination test(negative results for titers lower than 1:40) of a serum specimen. Test was performed at the discretion of pediatric attending physicians.

Chest radiographs were evaluated by three radiologists who were not involved with the clinical care of these cases.

Fever condition of those patients were collected, including the duration of fever before oseltamivir, duration of fever after oseltamivir, the highest body temperature during the course of fever, and the total duration of fever.

Fever was considered when a patient had a forehead temperature higher than 37.4℃. The duration of fever was defined as the period of time from when the patient’ s forehead temperature was higher than 37.4℃ until it was lower than the same degree. This period was measured in days. The highest forehead temperature was defined as either the highest forehead temperature measured during hospitalization or the highest forehead temperature measured before admission.

All febrile patients were treated with antipyretics, and all of the study patients were treated with oseltamivir since the day the H1N1 infection was confirmed by rapid antigen testing.

2.3 Statistical Analysis

SPSS Traditional Chinese Version 12.0 (Sinter Information Corp, SPSS Inc., Taiwan) was used. A P value of less than 0.05 was considered to be statistically significant.

We used Independent T test and One-Way ANOVA to compare means of the total duration of fever and the duration of fever after receiving oseltamivir between different groups in several variables, including age, sex, BMI, with and without coexisting medical conditions, with and without

abnormal chest X-ray findings, using antibiotics or not, days of fever before loading oseltamivir.

We used Bivariate Correlations to check the correlations between total fever duration and the highest forehead temperature, white blood cell count, C-reactive protein level. We also check the correlations between the duration of fever after oseltamivir and the aforementioned variables.

3.Results

3.1 Demographic Data

There were 109 samples collected in this study. Gender ratio was 1.4 : 1.0 (M:F); age ranged from 1 to 18 years old, less than 6 years old (n=14, 12.8%, M/F=6/8), 7 to 12 (n=60, 55.0%, M/F=35/25), 13 to 18 (n=35, 32.1%, M/F=23/12). There was no difference in age distribution between sex.

There were four groups according to the BMI : 16 underweight(14.7%, M/F=5/11), 49 normal (45.0% , M/F=28/21), 24 overweight (22.0%, M/F=18/6), and 12 obese (11.0%, M/F=10/2). Males had a higher overweight and obesity ratio ($p<0.05$).

3.2 Clinical Manifestations

The mean time from the onset of fever to H1N1 screening was 1.82 days, with a range from 1 to 6 days (1.82 ± 0.88). The total fever duration ranged from 1 to 7 days (5.01± 1.07), with 85% of patients between 3-5 days. The duration of fever after oseltamivir treatment was 2 days in 18.3% cases, 3 days in 45.9% cases, and 4 days in 27.5% cases; the mean time was 3.2 days (3.19 ± 0.90). More than 6% of cases had a persistent fever lasting over 4 days. During the course of illness for each patient, their highest forehead temperature ranged from 36.2℃ to 40.8℃, with 15% less than 38.0℃ and 10% higher than 40℃ (38.74±0.79).

(Table 1)
Table 1. Distribution for fever features

Day(s)	DFBOa n(%)	FDAOb n(%)	TFDc n(%)	HTd T	n(%)
1	43 (39.4)	2 (1.8)	-	<37℃	1 (9)
2	50 (45.9)	20 (18.3)	1 (0.9)	37-37.99℃	16 (14.5)
3	12 (11.0)	50 (45.9)	6 (5.5)	38-38.99℃	39 (35.5)
4	2 (1.8)	30 (27.5)	26 (23.9)	39-39.99℃	42 (38.2)
5	1 (0.9)	6 (5.5)	44 (40.4)	40-40.99℃	11 (10.0)
6	1 (0.9)	1 (0.9)	23 (21.1)	Missing	1 (0.9)
7	-	-	8 (7.3)		
8	-	-	1 (0.9)		
Mean±SD	1.82 ± 0.88	3.19 ± 0.90	5.01±1.067		

a: Days of fever before loading oseltamivir
b: Fever duration after oseltamivir
c: Total fever duration
d: The highest temperature

Twelve patients had coexisting medical conditions, including one congenital lumbar myelomeningocele, one mental retardation, one patent ductus arteriosis s/p coil occlusion, one atrial septal defect type I s/p(status post) operation, one severe fatty liver, one right glaucoma s/p(status post) operation,, and six thalassemias.

The percentage of respiratory symptoms and signs were: cough (98%), rhinorrhea (49%), sore throat (47%), and nasal obstruction (20%). 28% of the patients had only one symptom, 35.8% had any two symptoms, 30% had any three symptoms, and 6% had all four symptoms. Diarrhea was noted in 6% of the patients, nausea and vomiting in 12%, and abdominal pain in 5%. No gastro-intestinal symptoms were found in around 79% of the total samples. Other symptoms included headache (22%), myalgia (6%), and general malaise (14%).

3.3 Laboratory Findings

Seventy-seven percent of patient's WBC count was within normal range (4000~10000/μL). Seventy-five percent of patient's neutrophil percentage was over 65% of WBC count. Eighty-four percent of patient's lymphocyte percentage was less than 25%. Ninety-five percent of patient's monocytes percentage was over 6%. Eosinophil percentage less than 3% was noted in ninety percent of total samples.

Ninety-six percent of patients had CRP data; Sixty-nine percent were higher than normal, but only two of them were higher than 10 mg/dL. There was no correlation between CRP and highest forehead temperature during the course of illness or total fever days.

Sixty-two percent of patients received ALT test and abnormal findings were found in 3% of the tested patients. Forty-three percent of patients had AST test and abnormal findings were noted in 15% of the tested patients. Twenty-six percent of patients received CPK test; all test results were normal.

Seventy-three percent of patients had chest x-ray examination. About eighty percent had abnormal findings. There were no significant differences between the normal and abnormal groups in total fever duration and the fever duration after oseltamivir.

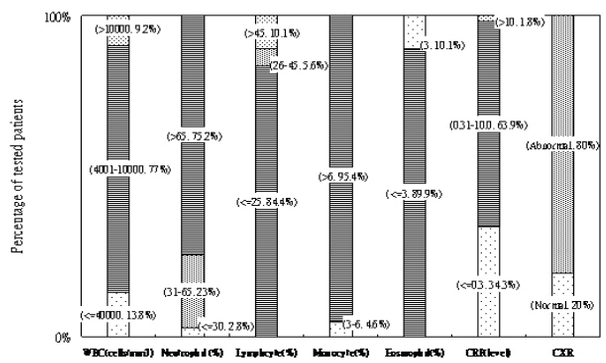

Fig 1 White blood cell counts and chest radiographs. (X, Y) X denotes total white blood cell count and percentage of four types of white blood cells; Y denoted the percentage of tested patients.

Sixteen percent of patients received urine analysis; 3 patients had abnormal findings, and one of them had microscopic hematuria (RBC count: 5-10//HPF). One of the other two had pyuria(WBC count: 10-20/HPF), and one had bactenuria (WBC count: 0-5/HPF, bacteria = ++), but urine culture results were negative. 13% received blood culture test but none had any findings.

Seventeen percent of patients received Mycoplasma antibody test. The abnormal finding rate was 61% with titers as follows: 2560X (+) (1), 320X (+) (1), 160X (+) (3), 80X (+) (5), and 40X (+) (1). All patients received antibiotics treatment except for 3 patients who had titers of 80X (+). In comparison with patients with a negative Mycoplasma antibody test result, there were no differences in age, body mass index, total fever duration, fever duration after oseltamivir, white blood cell counts, and CRP levels. In cases with abnormal CXR findings, 19% received Mycoplasma antibody test and the positive rate was 67%. 80% of patients with a positive Mycoplasma antibody test had abnormal chest x-ray findings.

3.4 Treatment

All patients received oseltamivir treatment. Forty percent of patients received oseltamivir on the first day of fever, 46% on the second day, and 11% on the third day. Ninety-seven percent of patients were treated within the first 3 days of fever. The average days of fever before loading oseltamivir was 1.88 days. (1.82±0.88)

The correlation between total fever duration and days of fever before oseltamivir treatment was significant ($p < 0.05$) either in antibiotic treated or untreated group. For antibiotic treated patients, the average duration of fever was 4.90 days if oseltamivir was given on the first day of fever (4.90±0.99), 5.45 days if given on the second day(5.45±0.83), and 6.38 days if given on or after the third day(6.38±0.74) ; for antibiotic untreated patients the average duration of fever was 4.21 days if oseltamivir was given on the first day of fever (4.21±0.96), 5.07 days if given on the second day(5.07±0.64), and 5.75 days if given on or after the third day(5.75± 1.28)

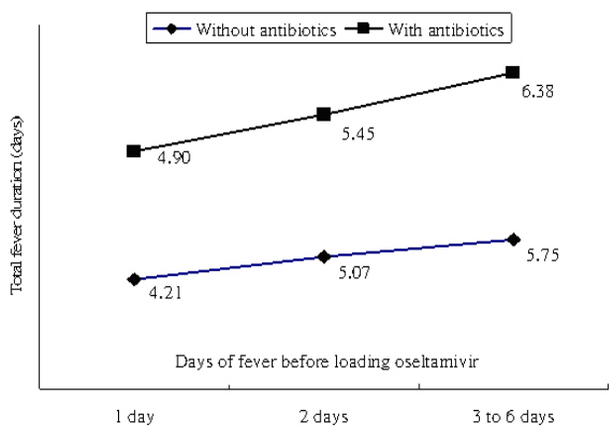

Fig 2. Trends in total fever duration

Sex, age, body mass index, white blood cell counts, CRP levels, coexisting conditions, and highest forehead temperature were not significant factors associated with total fever duration.

Only the highest forehead temperature was a significant factor associated with the fever duration after oseltamivir treatment. We found that higher forehead temperatures correlated with longer fever durations (pearson correlation coefficient = 0.36, $P<0.05$). Sex, age, body mass index, white blood cell counts,

CRP levels, coexisting conditions, and the day when oseltamivir was administered was not associated with the fever duration after oseltamivir.

Thirty-five percent of patients were treated by antibiotics. The total fever duration of patients who received antibiotics was significantly longer than that of untreated patients (mean of 4.50 days versus 3.75 days, $P < 0.05$). We found the fever duration after oseltamivir treatment between these two groups to be the same (mean 3.47 days versus 3.04 days, $P < 0.05$).

4.Discussion

In this article, samples were collected from a regional hospital in Taichung City that predominantly treated patients from Taichung's central district. During H1N1's pandemic stage, the pediatric department provided first-line care and counseling. Severe cases were not referred to our hospital. All patients admitted to our hospital were classified as mild to moderate and their course of illness did not develop to severe or result in mortality.

Our experience treating non-severe H1N1 cases in a regional hospital could give primary care physicians, who have fewer opportunities to care for severe cases, more details regarding the clinical courses of patients with non-severe H1N1.

We didn't use reverse transcriptase-polymerase chain reaction to identify the novel H1N1 influenza infection, but Taiwan's CDC reported the prevalence of novel H1N1 subtype in influenza A to be 86 to 100% during our sampling period. The prevalence of novel H1N1 was higher than 99% at the end of this research[6].

Sudden onset of fever (tympanic temperature ≧38°C) plus respiratory tract symptoms is one of the two criteria of influenza-like illness[7].Taiwan's CDC screening policy suggests an H1N1 screening test only for patients with a body temperature of 38°C or above[8].However, in our study 15% of patients had highest forehead temperatures less than 38.0°C. Therefore we suggest Influenza (A+B) Antigen tests for patients of mild fever, but with influenza-like illness or a contact history with a laboratory-confirmed infection in other family members or classmates.

In this study, over 75% of patients had a normal total white blood cell count. Granulocytosis, lymphocytopenia, and eosinopenia and monocytosis could be found in most cases. In fact, over 80% of our patients had lymphocytopeia, which was similar to the result(92.3% of children) of one study in China[9],near 90% had eosinopenia, and over 95% had monocytosis.

A total of 360 inpatients were studied at a medical center in northern Taiwan[10]. Their data revealed that presence of elevation of CRP level was independently associated with development of complications in patient with influenza. In our study, some patients had a CRP level that was higher than referential data, but in most cases it was not significant, and none of our patients developed complications over the course of illness. Our result confirmed their finding from an opposite point of view.

There have been studies proven that bacterial infection has a role in severe cases of H1N1[11,12,13].Most of these studies do not analyze data regarding Mycoplasma infection. One study concluded that there is no evidence of a synergistic co-infection of influenza A with Mycoplasma pneumoniae or other agents of atypical pneumonia in fatal H1N1 cases[12].

In our study physicians arranged a first mycoplasma Ab test when a patient had dyspnea, persisted cough, or persisted fever even after anti-viral treatment. The positive rate of mycoplasma antibody test was over 60% in tested patients, and anti-mycoplasma antibiotics were administered. We could not prove the co-infection of mycoplasma because the parents hesitated to let their children receive a 2nd mycoplasma Ab test when clinical improvements were seen. Further study is needed to explore the role of Mycoplasma infection in novel H1N1 influenza.

Abnormal CXR findings such as interstitial abnormalities, local patchy shadowing, ground-glass opacities were present in more than 80% of the patients in the study. This shows that these findings are common in non-severe cases of H1N1 infection[14,15].The results are similar to a study done by a medical center

involving 43 pediatric inpatients. 63% patients had a CXR showing diffuse multilobar infiltration and 16% showed a pneumonia patch for a total of 79% patients with abnormal CXR findings[16].In comparison with another study in Argentina involving patients younger than 18 years old, the percentage of focal pneumonia was 33% and multifocal pneumonia was 45% for a total of 78%, which is consistent with our results[17].

Abnormal CXR findings in our samples are higher than results of China's (cases quarantined at the airport, 26% with an age less than 14) 5.1%[9], and USA's (inpatient's, not in ICU, 48% with an age less than 18) 28%[2].

H1N1 patient's with abnormal chest x-ray findings had no distinguishing clinical features, fever courses, or laboratory findings. This phenomenon may be due to the fact that all CXRs were evaluated by radiologists who have little experience with pediatric x-rays. While adult CXRs are typically very clear, children tend to present with varying degrees of lung infiltration that usually are of no clinical significance.

97% patients in our study received oseltamivir within their first three days of fever, and all our cases were non-severe. The outcome provides clinical evidence to support one study conducted at a medical center in northern Taiwan, concluding that delaying antiviral therapy with oseltamivir may contribute to an increased severity of illness[10].Comparing a case series of 18 patients hospitalized in Mexico city from March 24 through April 24, 2009, our patients had shorter mean days from illness onset to viral testing (1.82 vs. 9), had shorter mean days to receive oseltamivir after the onset of symptoms (1.82 vs. 8), and a far more less percentage of death (0% vs. 45%)[1].

In our study, we found that the shorter the interval from fever onset to oseltamivir therapy, the shorter the total fever duration. The total fever duration of patients with interval of one day would have a total fever duration that was on average 0.85 days shorter than that of patients with an interval of two days. Likewise, the total fever duration of patients with an interval of two days was 0.53 days shorter than that of patients with an interval of three days. Our findings coincided with one study in China, which concluded that the duration of infection, as was confirmed by real-time RT-PCR, may be shortened if oseltamivir is administered[9].

There are some limitations in this research. First, all evaluations and surveys were clinically driven, not an experimental design study, and so some missing data may interfere with analysis. Second, there was no control group such as samples from ambulatory cases, limiting the results to apply only to hospitalized cases. Third, there is an inherent bias that may lead to the underestimation of the duration of fever due to some patients not measuring their own forehead temperature during the initial days of illness.

5.Conclusions

In summary, most non-severe H1N1-infected pediatric patients in our study presented with lymphocytopenia, monocytosis, eosinopenia, and abnormal chest x-ray findings. Fever less than 38°C could not be a decision factor not to screen for novel H1N1 because more than 10 % patients had their highest temperature less than 38°C during their illness course. The rate of positive mycoplasma antibody test was high in our tested group. The shorter the interval from fever onset to oseltamivir therapy, the shorter was the total fever duration either for antibiotic treated or untreated patients.

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Disclosure Statement

Authors have no conflict of interest.

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台灣中部區域型教學醫院小兒科H1N1新型流感住院病例分析

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摘要

疾病管制局於2009年6月發佈台灣第一個實驗室診斷確認的新型H1N1病例，A型流行性感冒病毒 (H1N1)逐漸造成台灣島內全面的大流行；本文回顧本院109位小兒科新型H1N1非重症住院個案的病歷(自2009年8月19日到2009年12月28日)，所有病人皆在流行性感冒病毒A型+B型快速診斷檢查確定陽性後入院；百分之十五個案的最高額溫未超過攝氏38度，百分之八十四個案的淋巴球比例低於25%，百分之九十五個案的單核球比例高於6%，百分之九十個案的嗜酸性白血球比例低於3%；百分之十七的個案接受黴漿菌抗體試驗，其中的百分之六十一高於正常值；百分之七十三的個案胸部X光檢查報告為異常；所有的病人皆接受抗病毒藥oseltamivir治療，其中的百分之九十七在發燒開始的三天內開始服用；第一天就開始服用oseltamivir的個案平均發燒持續時間是4.37天，第二天開始服用個案的平均發燒時間是5.22天，第三天後才開始服用的個案平均發燒時間6.06天；百分之三十五個案接受抗生素治療，平均發燒天數顯著比未接受抗生素治個案長；最高額溫是唯一和服用oseltamivir後發燒持續時間有正相關的因子。

大多數新型H1N1非重症的小兒科個案表現淋巴球減少、嗜酸性白血球減少、單核球增加及胸部X光報告異常；因高達百分之十五個案的最高額溫未超過攝氏38，因此最高額溫未超過38度不應做為不篩檢的決定因素；本研究個案越早服用oseltamivir，發燒持續時間越短。

關鍵詞：新型流感、H1N1、oseltamivir