EARLY ADMINISTRATION OF OSELTAMIVIR WITHIN 48 HOURS AFTER ONSET OF FLULIKE SYMPTOMS CAN REDUCE THE RISK OF INFLUENZA B VIRUS-ASSOCIATED PNEUMONIA IN HOSPITALIZED PEDIATRIC PATIENTS WITH INFLUENZA B VIRUS INFECTION

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Abstract: We conducted a retrospective study to identify the risk factors for pneumonia in hospitalized pediatric patients with influenza B infection. Receiving oseltamivir within the first 48 hours of onset and frequent cough was respectively considered as a protective factor and a risk factor for the influenza B virus-associated pneumonia in hospitalized pediatric patients. Early administration of oseltamivir can reduce the risk of influenza B virus-associated pneumonia.

Key Words: influenza B, pneumonia, risk factors, pediatric patients, oseltamivir

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Outbreaks of influenza B occurred from November 2017 to April 2018 worldwide. Annual seasonal influenza epidemics, which were caused by influenza virus A and B, are associated with enormous health and economic consequences worldwide[1] and are estimated to cause about 3–5 million cases of serious diseases, and about 250–500,000 deaths each year.[1,2] Among US pediatric influenza deaths between 2004 and 2011, excluding the 2009–2010 pandemic, 22%–44% of deaths, each season, were confirmed to be related with influenza B.[3] Among the cases of death, 35% were complicated with pneumonia.[4] However, few data are available on the risk factors for influenza B virus-associated pneumonia in pediatric patients. The incidence and mortality rate of pneumonia may be reduced if the risk factors for susceptibility to pneumonia are identified and high-risk patients are diagnosed and treated early in the course of the disease. Therefore, we conducted a retrospective study of pediatric patients who had been diagnosed with influenza B infection at our institution from November 1, 2017 to April 1, 2018 to investigate demographics, clinical characteristics and laboratory findings and to determine the risk factors of influenza B virus-associated pneumonia.

METHODS

Study Population and Design

This was a retrospective observational study which approved by the Ethics Committee of hospital. Patients were identified using our hospital computerized medical records system database from 1 November 2017 to 1 April 2018. Patients admitted during the study period who met all the following criteria were included: (1) age <18 years old; (2) presenting with 1 or more influenza-like symptoms (fever, cough, rhinorrhea, sore throat, muscular soreness, hoarseness, headache, shortness of breath, digestive tract symptom); (3) complete data of blood test (complete blood count, C-reactive protein, liver function, kidney function, serum electrolytes) and chest radiographs obtained within 24 hours of hospital admission; (4) influenza B infection confirmed by a reverse-transcriptase polymerase chain reaction assay from nasopharyngeal swabs or oropharyngeal swabs.

Pneumonia was diagnosed based on clinical features and a chest radiograph. All chest radiograph were reviewed by a radiologist who confirmed the diagnosis. Pneumonia was defined radiographically by the modified World Health Organization criteria as the criteria as the presence of a consolidation, infiltrate or opacities that could be described as alveolar, interstitial or lobar.

Cough Symptom Score (CSS) was used to assess cough frequency and severity. CSS consists of 2 questions regarding subjective cough severity during the day and in the evening. The patients >10 years old were asked to self-assess their cough, and the same in patients under 10 years old was assessed by their parents. Frequent cough was defined when cough scoring ≥3 during daytime and/or nighttime.

Data Collection

During the study period, for patients presented to the Accident and Emergency Department (AED) with influenza-like illness (ILI), that is, fever plus 1 or more symptoms of cough, rhinorrhea, sore throat, myalgia, hoarseness, headache or shortness of breath, nasopharyngeal or oropharyngeal swabs should be taken for reverse-transcriptase polymerase chain reaction assay. Blood tests and chest radiographs should be done according to the AED clinician's clinical judgment. Depending on the clinical features of a patient, the AED clinicians had the right to admit the patient. All patients admitted with ILI should have a chest radiograph performed. The chest radiographs might be repeated after hospitalization. All films were reviewed and reported by the radiologists within 48 hours. Patients hospitalized for ILI during the study period were recruited in this study. They were identified from the hospital database with the principal diagnosis of ILI, chest infection or pneumonia. The following variables were collected: demographic characteristics of patients, the time of onset, the time of diagnosis and treatment, underlying conditions, clinical characteristics, CSS, and radiologic findings, laboratory data, influenza virus data and the treatment outcomes.

Statistical Analysis

For categorical variables, proportions were compared using Fisher's exact test or the χ^2 test, as appropriate. Continuous variables were analyzed with the Student's *t* test. A two-tailed *P* value of <0.05 was considered significant. Multivariate analysis was performed using logistic regression. A significance level of <0.05 was used in this test. All analyses were performed using SPSS version 13 (IBM SPSS, Chicago, IL).

RESULTS

Between November 1, 2017 and April 1, 2018, a total of 275 patients with influenza B virus infection were hospitalized and monitored. Only 215 patients have complete data, of which 78 patients were adults and 137 patients were <18 years of age. Among the 137 patients, 54 patients were females (39.4%), 83 were males (60.6%) and the mean age ± standard deviation was 4.39±3.15 years (range, 1 month–15 years). The majority of the patients were in the age group 2–5 years (35.0%) and 5–9 years (32.1%). Of these patients, 54 patients (39.4%) with pneumonia were identified. Table 1 summarizes the distribution of underlying conditions. No patients died in the period of hospitalization.

TABLE 1. Comparison of Clinical Features of Influenza B Virus Infection Between Patients Combined With and Without Pneumonia

Variable	With Pneumonia (n = 54)	Without Pneumonia (n = 83)	Overall (n = 137)	*P*
Demographics				
Female gender, no (%)	26 (48.1)	28 (33.7)	54 (39.4)	0.092
Age in years, mean ± SD	4.0 ± 2.5	4.7 ± 3.5	4.4 ± 3.2	0.169
Age group, no (%)				
0–4 years	34 (63.0)	45 (54.2)	79 (57.7)	0.311
5–9 years	19 (35.2)	30 (36.1)	49 (35.8)	0.909
10–18 years	1 (1.9)	8 (9.6)	9 (6.6)	0.148
Presence of ≥1 underlying conditions, no (%)				
Asthma	1 (1.9)	5 (6.0)	6 (4.4)	0.460
Leukemia	0 (0)	3 (3.6)	3 (2.2)	0.415
Diabetes mellitus and metabolic diseases	0 (0)	1 (1.2)	1 (0.73)	1.000
Transplantation	0 (0)	1 (1.2)	1 (0.73)	1.000
Renal diseases	1 (1.9)	0 (0)	1 (0.73)	0.394
Liver diseases	1 (1.9)	0 (0)	1 (0.73)	0.394
Nonmalignant hematopathy	0 (0)	5 (6.0)	5 (3.7)	0.170
Low birth-weight	2 (3.7)	2 (2.4)	4 (2.9)	1.000
No underlying diseases	51 (94.4)	69 (83.1)	120 (87.6)	0.050
BMI kg/m^2	15.9 ± 2.4	15.8 ± 2.3	15.9 ± 2.3	0.731
Day from onset of symptoms to ED	4.2 ± 1.8	2.9 ± 2.4	3.4 ± 2.3	0.001
Received oseltamivir within the first 48 hours of onset, no (%)				
Age group received oseltamivir within the first 48 hours of onset, no (%)	4 (7.4)	37 (44.6)	41 (29.9)	0.000
0–4 years	3 (5.6)	22 (26.5)	25 (18.2)	0.002
5–9 years	1 (1.9)	12 (14.5)	13 (94.9)	0.014
10–18 years	0 (0)	3 (3.6)	3 (2.2)	0.415
Dose of oseltamivir use within the first 48 hours of onset, mg/kg*	2.6 ± 0.4	2.4 ± 0.8	2.5 ± 0.9	0.610
Use of antibiotics before hospital admission, no (%)	16 (29.6)	13 (15.7)	29 (21.2)	0.051
Influenza vaccination during most recent season, no (%)	4 (7.4)	7 (8.4)	11 (8.0)	1.000
Symptoms and signs at hospital admission, no (%)				
Fever	52 (96.3)	77 (92.8)	129 (94.2)	0.626
Frequent cough	49 (90.7)	54 (65.1)	103 (75.2)	0.001
Rhinorrhea	23 (42.6)	30 (36.1)	53 (38.7)	0.449
Sore throat	2 (3.7)	6 (7.2)	8 (5.8)	0.626
Hoarseness	2 (3.7)	2 (2.4)	4 (2.9)	1.000
Muscular soreness	1 (1.9)	4 (4.8)	5 (3.7)	0.661
Headache	1 (1.9)	4 (4.8)	5 (3.7)	0.661
Shortness of breath	1 (1.9)	2 (2.4)	3 (2.2)	1.000
Digestive tract symptom	6 (11.1)	19 (22.9)	25 (18.3)	0.081
Abnormal breath sounds on auscultation	11 (20.4)	9 (10.8)	20 (14.6)	0.123
Serum CRP level, mg/L	18.1 ± 18.0	9.4 ± 15.6	12.8 ± 17.1	0.004

*The usage of oseltamivir oral suspension: the doses were 75 mg twice daily in those weighing >40 kg; 60 mg twice daily in those weighing >23–40 kg; 45 mg twice daily in those weighing >15–23 kg; and 30 mg twice daily in those weighing ≤15 kg.

ED indicates Emergency Department.

For the 137 hospitalized pediatric patients with influenza B virus infection, their characteristics and laboratory findings were compared between cases with and without pneumonia (Table 1). Patients with pneumonia had significant in the day from onset of symptoms to emergency department ($P = 0.001$), the rate of received oseltamivir within the first 48 hours of onset ($P = 0.000$). The pneumonia group was also significantly higher rate of frequent cough ($P = 0.001$), higher level of serum CRP ($P = 0.004$), the rate of age group (0–4 years) received oseltamivir within the first 48 hours of onset ($P = 0.002$), and the rate of age group (5–9 years) received oseltamivir within the first 48 hours of onset ($P = 0.014$) than the non-pneumonia group. No significant difference was observed in the rate of gender, age group, underlying conditions, use of antibiotics before admission and recent injection of influenza vaccine between the 2 groups. BMI, age, symptoms, dose of oseltamivir use per body weight within the first 48 hours of onset and other laboratory findings, except serum CRP level, were similar in both groups.

The 6 variables including day from onset of symptoms to emergency department, received oseltamivir within the first 48 hours of onset, age group (0–4 years) received oseltamivir within the first 48 hours of onset, age group (5–9 years) received oseltamivir within the first 48 hours of onset, frequent cough, and serum CRP level identified to be significant were entered into a multivariate analysis. By logistic regression models, received oseltamivir within the first 48 hours of onset (OR, 0.108; 95% CI: 0.035–0.334; $P = 0.000$) and frequent cough (OR, 2.153; 95% CI: 1.257–3.689; $P = 0.005$) were significantly associated with pneumonia.

DISCUSSION

Oseltamivir was a neuraminidase inhibitor (NAI) and was used worldwide for treatment and prophylaxis of influenza caused by influenza A and B viruses. NAIs can alleviate the major symptoms of uncomplicated influenza A and B and reduce the duration when administered within 48 hours of onset of illness compared with a placebo.[5] Garg et al[6] reported that antiviral therapy started at >48 hours after the onset of symptoms tends to be more common in patients with pneumonia or other influenza complications than in those without among patients with influenza A. But another study[7] suggested that oseltamivir is ineffective against influenza B and is influenced by age or the immunity of the host. A prospective, multicenter observational study[8] of the 2003–2004 and 2004–2005 influenza seasons, in Japan

showed that oseltamivir is less effective against influenza B than influenza A, but oseltamivir was more effective compared with patients with influenza B infection who were not treated with an anti-influenza medicine. The study[8] revealed oseltamivir would reach its best effect in patients with influenza B in older children (age: 7–15 years), and speculate the reason was that routine dosage of oseltamivir given to children <7 years or adults ≥16 years of age may be insufficient to effectively inhibit influenza B virus replication. However, a recent study also conducted in a Japan pediatric clinical during 3 influenza seasons (2014–2017) showed that NAIs (including oseltamivir) were more effective in patients with influenza B in older children than younger children (age, 10–18 years > 5–8 years > 0–4 years).[9] What might account for the conflicting results of these studies? One source of variation maybe the differences in criteria and primary efficacy endpoints these studies used for analysis; another reason may be that the NAI-resistance of influenza B virus was not detected in all the above studies, which would inevitably lead to bias. Antiviral surveillance studies conducted during different seasons and in different geographic areas have shown the number of NA mutations in influenza B viruses acquired as a result of drug selection pressure or natural drift was growing year by year,[10] which presented a challenge for anti-influenza treatment. The latest research conducted during the 2017–2018 winter influenza season in Beijing carried out identification of NAI drug resistance mutations and showed that the current antiviral protocol was still effective for influenza B control.[11] In aggregate, the data suggested that oseltamivir was effective at treating influenza B infections. In our study, there was no significant difference in age distribution and the dosage of oseltamivir use per body weight within the first 48 hours of onset between pneumonia group and non-pneumonia group, and our findings show that early application of oseltamivir (started at ≤48 hours) was a protective factor for influenza B-associated pneumonia in the pediatric patients, compared with those patients started at >48 hours, while age group received oseltamivir within the first 48 hours of onset was not significantly associated with incidence of influenza B virus-associated pneumonia in our study. During influenza B epidemic season, when patients have flu-like symptoms, early use of oseltamivir can reduce the complications of pneumonia. Clinical features independently associated with pneumonia in patients with pandemic influenza A H1N1 include dyspnea, wheezing, vomiting and diarrhea.[12] As shown in our study, frequent cough was a risk factor for influenza B-associated pneumonia in pediatric patient. The initial symptoms and sign at disease onset may better reflect patient characteristics in the onset of pneumonia and, to a certain extent, reflect the site of viral or bacterial infection. As the virus or bacteria infected the lower respiratory tract of pneumonia patients, leading to hyperemia, edema and increased mucus secretion of the respiratory mucosa, which will cause the symptoms and sign including frequent cough, expectoration, shortness of breath, wheezing, abnormal breath sounds on auscultation. In conclusion, received oseltamivir within the first 48 hours of onset was a protective factor, while frequent cough was a risk factor for the influenza B virus-associated pneumonia in hospitalized pediatric patients.

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IMPACT OF BASELINE TUBERCULIN SKIN TEST AND ISONIAZID CHEMOPROPHYLAXIS ON SUBSEQUENT QUANTIFERON-TB GOLD IN-TUBE PERFORMANCE IN YOUNG CHILDREN ASSESSED AFTER TUBERCULOSIS CONTACT IN CATALONIA

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Abstract: We investigated the impact of baseline tuberculin skin tests (TSTs) and preventive isoniazid chemoprophylaxis on subsequent QuantiFERON-TB Gold In-Tube (QFT-GIT) assays performed after a 10- to 12-week window period in 114 children <5 years of age. Previous TSTs and chemoprophylaxis had no impact on the magnitude of subsequent antigen-induced responses in QFT-GIT. Furthermore, previous TSTs did not induce conversion from a negative to a positive QFT-GIT result.

Key Words: infant, interferon-gamma release assay, isoniazid, tuberculin skin test, boosting

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