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RESEARCH ARTICLE / *ARAŞTIRMA MAKALESİ*

Influenza Infection in Infants Under One Year of Age

Bir Yaş Altı İnfantlarda İnfluenza Enfeksiyonu

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ABSTRACT

Objective: Influenza virus infections are infectious agents which lead to epidemics and pandemics, are associated with severe morbidity and mortality, and still maintain their importance worldwide. This study was planned due to the fact that influenza virus infections are associated with complications and hospitalizations in infants under 1 year of age.

Material and Method: 56 infants diagnosed with influenza between October 2017 and February 2018 were retrospectively evaluated.

Results: Mean age of the patients was 5.6±2.1 (2-11) months. Of the patients; 46.5% were followed-up in an inpatient setting and 53.5% in an outpatient setting. 22 patients were diagnosed by polymerase chain reaction method and 34 by rapid antigen test. Of the patients; 53.5% (n=30) were followed-up with diagnosis of upper respiratory tract infections, 33.9% (n=19) with pneumonia, 10.7% (n=6) with sepsis and 1.7% (n=1) with encephalitis. Mean duration of hospital stay was determined to be 8.32 (2-38) days.

Conclusion: Influenza virus infections cause a high rate of hospitalizations in infants younger than one year old, it is necessary to determine with fast and accurate diagnostic methods, to arrange their treatment and to provide appropriate isolation measures.

Keywords: Influenza, infant, polymerase chain reaction, rapid antigen testing

ÖZ

Amaç: İnfluenza virüs enfeksiyonları epidemi ve pandemilerle seyreden, ciddi morbidite ve mortalite ile ilişkilendirilen, halen dünya genelinde önemini koruyan bir enfeksiyon etkenidir. Bir yaş altı infantlarda influenza virüs enfeksiyonlarının hospitalizasyon ve komplikasyonlarla ilişkisi olması sebebiyle bu çalışma planlanmıştır.

Gereç ve Yöntem: Ekim 2017- Şubat 2018 tarihleri arasında influenza tanısı alan 56 infant retrospektif olarak değerlendirilmiştir.

Bulgular: Hastaların ortalama yaşı 5,6±2,1 (2-11) ay idi. Hastaların %46,5'i hastaneye yatırılarak, %53,5'i ayaktan takip edildi. 22 hastaya polimeraz sincir reaksiyonu yöntemiyle, 34 hastaya hızlı antijen testi ile tanı konuldu. Hastaların %53,5'i (n=30) üst solunum yolu enfeksiyonu, %33,9'u (n=19) pnömoni, %10,7'si (n=6) sepsis, %1,7'si (n=1) ensefalit tanısıyla takip edildi. Ortalama yatış süresi 8,32 (2-38) gün olarak saptandı.

Sonuç: İnfluenza virüs enfeksiyonları bir yaş altı infantlarda yüksek oranda hospitalizasyona sebep olmaktadır, hızlı ve doğru tanı yöntemleri ile belirlenerek tedavisinin düzenlenmesi ve uygun izolasyon önlemleri sağlanması gerekmektedir.

Anahtar Kelimeler: İnfluenza, infant, polimeraz zincir reaksiyonu, hızlı antijen testi

INTRODUCTION

Influenza A and B viruses are among the most common causes of severe diseases and deaths worldwide, affecting millions of people every year (1). Symptoms include fever, cough, nasal discharge, fatigue, myalgia and headache. Influenza viruses, which are very contagious and cause epidemics, continue their existence for a long period of time through making alterations in their antigenic structures and not evolving a permanent immune response. Epidemics and pandemics caused by influenza viruses are closely associated with susceptibility of individuals to the virus and virulence of the virus. Influenza-

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associated deaths still have an important place despite of many socio-economical advancements (2). Especially in infants under two years of age, rates of influenza infection-associated severe diseases and mortality are significantly increased (3). The aim of the study was to describe the clinical, laboratory and epidemiologic characteristics of patients under one year of age who were diagnosed with influenza during 2017-2018 autumn-winter period which is known to be high-severity influenza season with hospitalizations by the American Center for Disease Control and Prevention (CDC).

MATERIAL AND METHOD

56 infants under one year of age who presented with fever, cough and nasal discharge then diagnosed with influenza by rapid antigen tests or real-time polymerase chain reaction (PCR) method between October 2017 and February 2018 were retrospectively evaluated. Nasal and nasopharyngeal swab samples from the patients were taken to Copan Universal Transport Medium™ and sent to the Necmettin Erbakan University Meram Faculty of Medicine Virology Laboratory on the same day. Samples that could not be delivered to the laboratory on the same day were stored at 4-8°C and delivered to the laboratory within 48 hours at the latest. The extraction tube was placed in the workstation and 8 drops of extraction reagent were added. The samples were placed in the extraction tube. Swap was rotated for about 10 seconds. The dropper tip was placed in the extraction tube. The test cassette was placed on a clean and flat surface. 3 drops of solution were added to the sample well. Results were read after 8 minutes. If another line formed under the control line on the strip, the test was considered positive.

The EZ1 Virus Mini Kit V 2.0 (QIAGEN, Germany) was used for viral RNA extraction. The extraction process was performed on the EZ1 Advanced XL (QIAGEN, Japan) device according to the manufacturer instructions. Multiplex real-time PCR method was performed on RotorGene 5 Plex HRM (QIAGEN) using the FTD respiratory pathogens 21 (fast-tract diagnostics, Luxembourg) kit to diagnose Influenza A, Influenza B and subtype H1N1 (pandemic H1N1) viruses. 10 µl of RNA isolation samples were taken and mixed with 15 µl master mix in the PCR tube. A positive control and a negative control were used for each study. The PCR program was run for 40 cycles, the fluorescence measurements resulting from the amplification and the reactions were monitored in real time and the results were recorded. The test was recorded positive if there was a reaction in both the green channel (sample) and the red channel (internal control). The presence of a signal in the red channel in the absence of any signal in the green channel was considered a negative result. Since the result cannot be evaluated if there is no signal in both channels, the test was repeated.

The overall results of this study were expressed as percentages for categorical variables, and as means±SD, and medians for continuous variables.

RESULTS

A total of 56 patients (37 male, 19 female) under one year of age were diagnosed with influenza infection in the study period. Mean patient age was 5.6±2.1 (2-11) months. 12 (21.4%) patients were aged 1-3 months, 20 (35.7%) 3-6 months, 19 (33.9%) 6-9 months and 5 (8.9%) 9-12 months. A total of 2839 PCR tests were performed in children who were admitted to our hospital, of these; 274 were under one year of age, and 56 (20.4%) of them were PCR positive. Thirty-four (60.7%) patients had a family member with similar symptoms. Of the patients; 46.5% were followed-up as inpatient and 53.5% as outpatient. 22 patients were diagnosed by using PCR method and 34 patients by rapid antigen tests. Of the patients; 39 (69.7%) were diagnosed with Influenza A and 17 (30.3%) with Influenza B. Admission complaints, physical examination findings and laboratory findings of the patients are summarized in Table 1. Of the patients; 53.5% (n=30) were followed-up with diagnosis of upper respiratory tract infections, 33.9% (n=19) with pneumonia, 10.7% (n=6) with sepsis and 1.7% (n=1) with encephalitis. In a 3-month-old previously healthy patient who presented with complicated febrile seizure and weakness, cerebrospinal fluid (CSF) was clear and colorless with an opening pressure of 10 cm of H_2O and its microscopic examination showed 10/mm^3 cell counts with 100% lymphosit predominance with normal protein and glucose levels. Her cranial magnetic resonance imaging was normal. CSF cultures were bacteriologically sterile and she recovered without sequalae.

Laboratory results of the hospitalized patients were as follows: The mean total leukocyte count was 8,916/mm³ (range: 2,500-20,900/mm³), mean absolute neutrophil count: 3,736/mm^3

Table 1. Clinical and Laboratory Characteristics of the Patients

Complaint	n=56	%	Physical Examination	n=56	%	Laboratory findings	n=31	%
Fever	47	83.9	Tonsillar hyperemia	36	64.2	Leukocytosis	10	32.2
Cough	34	60.7	Tachypnea	21	37.5	Leukopenia	3	9.6
Nasal discharge	22	39.2	Rales- Rhonchi	24	42.8	Neutropenia	6	19.3
Unease	3	5.3	Hypoxia	4	7.1	Lymphopenia	1	3.2
Diarrhea	3	5.3	Cutis marmorata	3	5.3	Thrombocytopenia	4	12.9
Seizure	1	1,78	Bulging fontanel	3	5.3	Elevated CRP*	17	54.8

*C- reactive protein

(228- 10,000/mm^3), mean absolute lymphocyte count: 4,210/mm^3 (574- 8,300/mm^3), and the mean platelet count: 280,000/mm^3 (21,800-528,000/mm^3). The mean C-reactive protein (CRP) level of the study group was 19.53 mg/L (range: 5-87 mg/L). One patient had hypertransaminasemia and work-ups of this patient were suggestive of Alagille syndrome. Mean duration of hospital stay was determined to be 8.32 (2-32) days. The patient with the shortest duration of hospital stay was treated as inpatient for 2 days, and the patient with the longest duration of hospital stay was treated as inpatient for 38 days. Eleven of 12 patients (91%) between 1-3 months of age received inpatient treatment. Mean duration of hospital stay of infants under 3 months of age was 4.2 (2-8) days. Of these patients under three months of age; five were followed up with pneumonia, four with sepsis and one with encephalitis.

All of the patients were administered oseltamivir as antiviral treatment. Mean duration of fever was 2.24 days and time to reduction of fever after initiation of treatment was 0.84 days. 84% of the hospitalized patients were patients with no known disease. History of premature birth (3 patients), as well as presence of immunodeficiency (2 patients), cystic fibrosis (2 patients) and neuro-motor retardation (2 patients) were determined to be risk factors for prolonged hospitalization. During the study period, one patient died. The deceased patient had a history of operation for a tracheo-esophageal fistula and had syndromic facial appearance. He died on the 13th day of hospitalization while being followed-up in the intensive care unit on mechanical ventilation support.

DISCUSSION

Although the majority of patients with influenza virus infections have a self-limited mild-to-moderate uncomplicated disease, it can lead to infections with severe mortality and morbidity at all ages all over the world. In addition to respiratory complications, several complications due to direct and indirect effects on other body systems were associated with influenza virus infections (4). The presenting complaints of patients requiring hospitalization due to pandemic influenza in the United States of America (USA) were fever in 93%, cough in 83%, nasal discharge in 36%, myalgia in 36% and sore throat in 31% (5). Similarly, in our study, fever (83.9%), cough (60.7%) and nasal discharge (39.2%) comprised the most common presenting complaints.

Complications of influenza are usually associated with underlying chronic diseases. However, it can also lead to high mortality and morbidity in previously healthy infants. Older adults, young children, and pregnant women are at increased risk for influenza-associated morbidity and mortality. According to a population-based surveillance study conducted between 2003 and 2012 in the USA, 75% of the hospitalized patients under 12 months of age were reported to be previously healthy (6). It is known that influenza burden among children is higher among those aged <5 years, with the highest hospitalization rates typically in young infants. Children with chronic medical conditions are at increased risk for complications (7). In our study, 84% of the hospitalized patients were patients with no underlying disease. Duration of hospital stay varyied between 2-38 days. History of premature birth, as well as presence of immunodeficiency, cystic fibrosis and neuro-motor retardation were determined to be risk factors for prolonged hospitalization. Influenza-associated hospitalizations were higher among children aged <5 years, especially <1 year, and the lowest among individuals aged 5-24 years, and have a more severe course under one year of age, especially under 3 months of age, and can lead to high hospitalization rates (3-8). In our study, 91% (n=11) of 12 infants under 3 months of age received inpatient treatment. Mean duration of hospital stay of infants under 3 months of age was 4.2 (2-8) days.

Neurological complications of influenza are more common among children between six months to four years of age. Major neurological complications are encephalopathy, febrile convulsion and aseptic meningitis (9). Most influenza-associated encephalopathy cases have been generally reported among children, and those with seizures were more common among pediatric patients, but cerebrospinal fluid pleocytosis and fatality rate are higher among adults (10). A three-month-old patient who had fever, altered mental status and convulsion was followed-up with a diagnosis of encephalitis, recovered without sequalae in our study. In one study, among patients who had neurological findings, the most frequent complaints at admission, in descending order, were fever, altered mental status, vomiting, and seizures. Cerebrospinal fluid (CSF) analysis of 11 cases showed that only two cases had pleocytosis, and the recovery rate without sequelae was found to be 50% (11). Influenza-related neurological complications should be kept in mind for those who are admitted with neurological findings during the influenza season.

Hematological disturbances may occur during influenza infection. Generally, leucopenia, lymphopenia, neutropenia and thrombocytopenia are observed. In a study from Turkey with 31 pediatric patients, eight (25.8%) patients had leukopenia and six (19.4%) thrombocytopenia at the time of diagnosis of H1N1 infection (12). In our study, it was determined that 6 patients had neutropenia, 1 lymphopenia and 4 thrombocytopenia. In a study with previously healthy 152 patients presenting with influenza-like illness/ acute respiratory infection, patients with influenza virus had higher rates of elevated CRP than that of other viral agents (13). In our study, 54.8% of our patients were determined to have elevated CRP levels.

Influenza infections cause severe respiratory distress, requiring invasive and non-invasive respiratory support. In our study, 4 patients required nasal continuous positive airway pressure and 1 required mechanical ventilation support.

Oseltamivir is effectively used in the treatment of influenza, by inhibiting neuraminidase in influenza virus. It has been proven to reduce the duration and severity of the disease when it is initiated within 48 hours after the onset of symptoms (14). Although oseltamivir is approved for early treatment of uncomplicated influenza in outpatients by the

Food and Drug Administration, the American Academy of Pediatrics and the CDC also recommend it for the treatment of hospitalized children with influenza at all ages. Despite these recommendations, antiviral treatment of hospitalized children with influenza greatly varies (7). One study reported that antiviral treatment of hospitalized patients with laboratory-confirmed influenza increased during 2010-2015, and overall, 72% of pediatric patients received antiviral treatment, with the largest increase over time in young children aged <1 year (15). In our study, all patients who were followed-up either as inpatients or outpatients were given oseltamivir. Response to fever with oseltamivir treatment was observed in patients in our study.

CONCLUSION

A mortality rate of 1.7%, despite of limited number of subjects, suggests a relatively high mortality rate for such a prevalent infection. Especially in infants at high risk of hospitalization and disease severity, rapid and accurate diagnosis is important in regard to enabling early specific antiviral treatment and the implementation of appropriate isolation measures.

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