

Retrospective Evaluation of Children with Influenza Infection

Gripli Çocukların Retrospektif Değerlendirilmesi

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Abstract

Objective: This study aimed to review the general characteristics of influenza and evaluate the clinical and laboratory characteristics of patients with influenza hospitalized in our unit.

Methods: This is a retrospective, descriptive study. Between 01.01.2017 and 01.07.2020; 124 patients hospitalized with flu-like illness symptoms and found to have influenza virus in the respiratory viral panel were included in the study.

Results: The mean age of the patients was 4.85 ± 3.94 years, of which 27 (21.8%) were less than 2 years old, 42 (33.9%) were between 2 and 5 years old, and 55 (44.4%) were older than the 5-year-old age group. Although many patients were at high risk of influenza, only 3 (2.4%) were vaccinated. The most common complaints at presentation were fever ($n=121$, 97.6%) and cough ($n=109$, 87.9%). Respiratory distress was more common in patients <2 years compared with the other age groups ($p=0.046$; $p=0.002$). Underweight and overweight/obese patients required more intensive care admissions than normal weight patients ($p=0.003$ and $p=0.001$, respectively). Of all patients, 116 (93.5%) recovered without sequelae, 4 (3.2%) died.

Conclusion: Although influenza infection is an important problem in terms of morbidity and mortality among children with respiratory tract infections, our vaccination rates are not sufficient even in high-risk groups. Influenza is a significant and serious disease, especially in children <2 years. Obese and malnourished patients may require more frequent intensive care admissions.

Keywords: Influenza, pediatric, flu vaccine

Öz

Amaç: Bu çalışmada influenza virüsün genel özelliklerinin gözden geçirilmesi, kliniğimizde yatırılarak izlenmiş influenza hastalarının klinik ve laboratuvar özelliklerinin değerlendirilmesi amaçlanmıştır.

Yöntem: Çalışmamız retrospektif, tanımlayıcı bir çalışmadır; 01.01.2017-01.07.2020 tarihleri arasında, grip benzeri hastalık semptomlarıyla yatırılarak izlenen ve solunum yolu viral panelinde influenza virüs saptanan 124 hasta çalışmaya dahil edilmiştir.

Bulgular: Hastaların yaş ortalaması $4,85 \pm 3,94$ yılıdır, bunların 27'si (%21,8) <2 yaş, 42'si (%33,9) 2-5 yaş ve 55'i (%44,4) >5 yaş grubundaydı. İnfluenza açısından riskli grupta çok sayıda hasta olmasına rağmen sadece 3'üne (%2,4) influenza aşısı yapılmıştı. En sık başvuru yakınmaları ateş ($n=121$, %97,6) ve öksürüktü ($n=109$, %87,9). Solunum sıkıntısı <2 yaş hastalarda diğer yaş gruplarına göre daha sıkı ($p=0,046$; $p=0,002$). Düşük kilolu ve fazla kilolu/obezler, normal kilolulara göre daha fazla yoğun bakım yatışı gerektirdi (sırasıyla $p=0,003$ ve $p=0,001$). Hastaların 116'sı (%93,5) sekelsiz iyileşti, 4'ü (%3,2) eksitus oldu.



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Öz

Sonuç: İnfluenza, çocuklarda solunum yolu enfeksiyonları arasında morbidite ve mortalite açısından önemli bir sorun olmasına rağmen, yüksek riskli gruplarda dahi aşılama oranlarımız yeterli değildir. İnfluenza özellikle <2 yaş çocuklarda önemli bir hastalıktır. Obez ve malnütre hastalar daha sık yoğun bakım ihtiyacı gerektirebilir.

Anahtar Kelimeler: İnfluenza, pediatri, grip aşısı

Introduction

The World Health Organization (WHO) reports that before the coronavirus disease-2019 (COVID-19) pandemic period, approximately 1 billion patients were infected annually worldwide due to the influenza virus, of which, approximately 3-5 million cases were in severe disease, and 300,000-500,000 cases resulted in death⁽¹⁾. The influenza virus causes both the loss of workforce among parents and the attendance of school for children. It can also lead to economic losses caused by diagnostic and treatment cost due to the disease burden^(2,3). Although influenza symptoms are generally mild, they can cause severe complications and mortality, especially in patients with underlying chronic diseases and children aged 2 years of age^(4,5). Acute respiratory tract infections, which are among the most common epidemics, are characterized by serious clinical findings, especially in childhood, and are responsible for 1/5 of all deaths in children under 5 years of age⁽⁶⁾. It is known that approximately 20-60% of these diseases are caused by viruses; studies show that viral respiratory tract infections occur 5-6 times a year in the early stages of life. In general, influenza viruses are the most common agents are influenza viruses^(7,8).

Materials and Methods

The study was conducted at the Adnan Menderes University Faculty of Medicine, Department of Pediatrics, and Pediatric Intensive Care Unit between 01.01.2017 and 01.07.2020. In this study, we included pediatric inpatients who were admitted with influenza-like illness (ILI) symptoms for the last 10 days and were diagnosed with influenza virus according to the respiratory viral panel. Socio-demographic characteristics of patients (age, sex, body weight (underweight, normal, overweight/obese), breastfeeding status of those under 2 years of age, history of prematurity, chronic diseases, and medications they regularly use) were examined. Admission symptoms, length of stay, need for respiratory support, and intensive care, whether the patient received oseltamivir treatment or not, which day of infection, and whether the patient received antibiotic treatment or not, were examined.

Complications associated with influenza, length of hospital stay, laboratory investigations, respiratory viral polymerase chain reaction (PCR) results, clinical course, morbidity, and mortality rates were evaluated retrospectively.

Cases were grouped as <2 years, 2-5 years and >5 years to evaluate risk status according to the age specified in the literature. The presence of at least one of these symptoms; cough, sore throat, and shortness of breath, which are also included in the Global Influenza Hospital Surveillance Network data collection forum, as respiratory symptoms for patients over 5 years of age, the onset of these symptoms, and the presence of tachypnea for patients under 5 years of age were examined. Patients were classified into underweight, normal weight, and overweight/obese according to the WHO body mass index (BMI) scoring by age and gender.

Patients with acute otitis media, laryngitis, sinusitis, bronchiolitis, bronchitis, pneumonia, or asthma attacks after influenza were evaluated as respiratory system complications. Seizures and changes in consciousness, encephalitis, Guillain-Barré syndrome, behavioral or personality disorders, and central or peripheral nervous system involvement were evaluated as neurological complications^(9,10). Patients with pericarditis, myocarditis and rhythm disturbances were evaluated as cardiac complications⁽¹¹⁾. Hematological findings such as leukopenia, lymphopenia, and neutropenia are common after influenza and were evaluated as hematologic complications^(12,13).

Nasopharyngeal swab samples taken from patients who were sent to the Adnan Menderes University Faculty of Medicine Microbiology laboratory for the study of respiratory viral molecular panels. Nucleic acid extraction was performed using the Magnesia Viral DNA/RNA Extraction kit (Anatolia, Türkiye) in the Magnesia 16 (Anatolia, Türkiye) device, in line with the company's recommendations. Nineteen different viruses (influenza A, H1N1, influenza B) including nucleic acids belonging to influenza A (all types that cause infection in humans), influenza pandemic H1N1, and influenza seasonal H1N1 by multiplex real-time PCR using Bosphore Respiratory Pathogens Panel Kit (Anatolia, Türkiye), respiratory syncytial

virus (RSV) A, RSV B, enterovirus, parechovirus, parainfluenza 1,2,3,4; metapneumovirus, adenovirus, bocavirus, rhinovirus, coronavirus 229E (OC43,NL63, HKU) nucleic acid presence were investigated.

Statistical Analysis

After all data were recorded on the computer, statistical evaluation was performed using the SPSS "Statistical Package for Social Sciences" (SPSS Inc. Chicago IL v 22.0. mean $\pm$ standard deviation, median, minimum, and maximum values were given in descriptive statistics for continuous data, and percentage values were given in discrete data. $P < 0.05$ was accepted as the threshold for statistical significance.

Prior to the study, permission was obtained from the Ethics Committee of Aydın Adnan Menderes University (number: 48843899-804.01, date: 24.07.2020).

Results

Nasopharyngeal swab samples from a total of 817 pediatric patients were obtained between the specified dates, and 124 patients with influenza A and/or B virus infection were included in the study. The mean age of the patients was 4.85 ± 3.94 years, and the female/male ratio was 0.72. Of all the patients with influenza, 27 (21.8%) were < 2 years old, 42 (33.9%) were 2–5 years old, and 55 (44.4%) were > 5 years old. The highest number of patients was seen in 2020 ($n=44$, 35.2%), and the highest positivity rate in all years was observed in January ($n=94$, 75.8%).

Thirty-eight (30.6%) patients had family members with ILI symptoms at home, and no patient stayed in a nursing home. Fifty-four (43.5%) patients were going to school/nursery. Sixty-five patients (52.4%) had at least one concomitant chronic disease, with the most common being chronic lung disease ($n=23$, 18.5%). Neurological and hemato-oncological

diseases followed this group. Of the patients in our study, 25.8% were underweight and 9.7% were overweight or obese. Prematurity was present in 16.9% of patients in our study cohort (Table 1). Only 3 (2.4%) patients were known to have the influenza vaccine.

The most common complaints were fever ($n=121$, 97.6%) and cough ($n=109$, 87.9%) (Figure 1). The most common laboratory findings were elevated C-reactive protein (> 5 mg/dL) ($n=64$, 51.6%) and lymphopenia ($n=39$, 31.5%). Influenza A PCR was positive in 84 (67.7%) and B PCR were positive in 40 (32.3%) patients. More than one virus was detected in 22 of the patients with influenza A and 11 with influenza B. The most common viral strain associated with influenza was RSV ($n=11$, 36.3%).

When analyzing the relationship between symptoms and viral agent, 10 (34.5%) of the patients with influenza B, 8 (12.9%) of the patients with influenza A, and only 1 (3%) of the patients who were found to have more than one virus. Myalgia was more common in patients with influenza B than in those with influenza A and more than one virus group ($p=0.01$ and $p=0.002$, respectively). Elevated creatine kinase (CK) (> 200 U/L) was detected in 38.7% of patients in our study. However, no significant relationship was observed between influenza subtypes and high CK ($p > 0.05$).

In our study, the probability of experiencing respiratory distress in patients < 2 years of age was higher than those in the 2–5 age group and > 5 age group ($p=0.046$ and $p=0.002$, respectively). In addition, the number of patients with more than one virus in the < 2 age group (59.3%) was higher than those aged 2–5 (26.2%) and those aged > 5 (10.9%) ($p=0.004$ and $p < 0.0001$).

Oseltamivir was initiated in 79 (63.7%) patients, and antibiotics were initiated in 93 (74.4%) patients due to secondary bacterial infection [most frequently secondary

Table 1. Risk factors of cases in terms of having influenza

	Number of patients	Percentage
Presence of people going to school/nursery at home	82	66.1
Presence of smoking individuals at home	68	54.8
Presence of chronic disease	65	52.4
School/nursery attendance	54	43.5
Presence of individuals with similar symptoms at home	38	30.6
< 2 years of age	27	21.8
Prematurity	21	16.9
Obesity	12	9.7

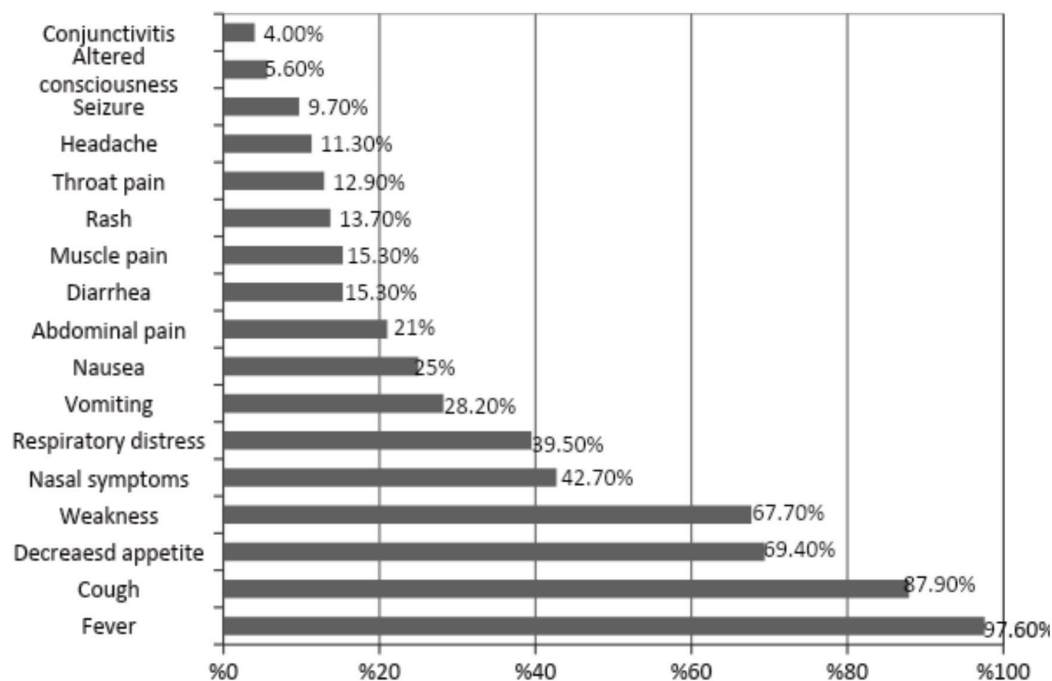


Figure 1. Patient complaints on admission

bacterial pneumonia (52.0%)). The most common antibiotic was ceftriaxone. The most common complication was respiratory system complications ($n=97$, 78.2%). Thirty-one (24.8%) patients required respiratory support, and 27 (21.6%) patients required intensive care at the time of hospitalization or during hospital stay. 10% of the patients with normal body weight, 40.6% of the underweight, and 50% of the overweight/obese patients were admitted to the intensive care unit. Underweight and overweight/obese patients were found to need more intensive care than those with normal body weight ($p=0.003$ and $p=0.001$, respectively). However, as a result of Spearman's correlation analysis, the correlation coefficient was found to be -0.118 , which showed us that there was no significant correlation.

In our study, the median length of stay in pediatric services was 3 days (1-31), and the median length of stay in intensive care units was 5 days (2-90). In patients who were started on oseltamivir in the first 48 hours, the mean length of hospital stay in pediatric service was 5 days (2-90) and the intensive care unit length of stay was 3 days (1-20), whereas those started after 48 hours were 6 (2-17) and 3 (1-31), respectively. There was no significant relationship between the time of initiation of oseltamivir and the duration of hospitalization in the service-intensive care unit ($p>0.05$).

In our study, when factors such as sex, prematurity, breastfeeding under 2 years of age, exposure to passive cigarette smoke were compared to influenza complications and the need for intensive care admission, it was found that there was no statistically significant relationship ($p>0.05$). During follow-up, 116 (93.5%) patients recovered without sequelae, whereas 4 (3.2%) patients died (Table 2). All patients who died in our study were found to be influenza A (H1N1) positive. There was no significant relationship between viral agent type and morbidity and mortality. As a result of the Pearson chi-square test, the p -value was 1,182, and no statistically significant difference was found. According to these results, when the number of patients presenting with fever and respiratory complaints increases during a certain period, especially in the winter months, it should be considered that influenza positivity may be present, and appropriate treatments should be selected by conducting tests accordingly. Therefore, unnecessary antibiotic and antiviral use can be prevented.

Discussion

Although the whole world is currently under the influence of the COVID-19 pandemic, influenza, which has caused significant economic and social problems, sequelae, and deaths, remains one of the most important viral pathogens.

Table 2. Clinical follow-up of patients

Clinical follow-up of patients	Number of patients	Percentage
Patients who started oseltamivir	79	63.7
Within 0-24 h of admission	28	22.8
Within 24-48 h of admission	13	10.6
>48 h of admission	38	30.9
Patients started on antibiotics	93	74.4
Complications developed in patients during follow-up		
Respiratory system	97	78.2
LFT changes	16	12.9
Neurological	15	12.1
Myositis	13	10.5
Hematologic	8	6.5
Sepsis/MOD	7	5.6
Cardiological	2	1.6
Others	4	3.2
Patients in need of respiratory support	31	24.8
Oxygen support	15	12.1
Mechanical ventilation	16	12.9
Patients who need intensive care during hospitalization/follow-up	27	21.6
Neonatal intensive care	3	2.4
Pediatric intensive care	24	19.2

LFT: Liver function tests, MOD: Multiple organ dysfunction

Most influenza cases examined in this study were children <5 years. It has been reported by the centers for disease control and prevention (CDC) that children younger than 5 years, especially those under 2 years, are among the highest risk groups for influenza-related hospitalization and development of serious complications⁽³⁾. In our study, respiratory distress was more common in patients aged 2 years compared to other age groups. In a meta-analysis, it was estimated that 28,000-111,500 children under the age of five died in developing countries due to influenza-related acute lower respiratory tract infection⁽¹⁴⁾. In another meta-analysis, influenza-related hospitalizations under the age of 5 were estimated to be approximately 870,000 per year worldwide, and 10% of general hospitalizations under the age of 18 due to respiratory distress were related to influenza infection⁽¹⁵⁾. In the study of Çiftçi et al.⁽¹⁶⁾ it was stated that respiratory distress is less in children older than five years, as in our study.

In our study, the probability of detecting more than one virus in patients aged 2 years was higher than that in other age groups. In a study conducted in Poland, including adult and pediatric patients, it was emphasized that influenza co-

infection was more common, especially in patients aged >65 years and in early childhood⁽¹⁷⁾. Similarly, in the study conducted by Kockuzu et al.,⁽¹⁸⁾ the mean age of patients with only influenza was 41 (11-75) months, whereas the mean age in the group positive for non-influenza viruses was 10 (3.5-28) months. In our study, the higher incidence of respiratory distress in the group of children aged 2 years suggested that it may be related to the higher incidence of co-infection in this age group.

In our study, underweight and overweight/obese patients were found to need more intensive care than those with normal body weight. However, as a result of Spearman's correlation analysis, the correlation coefficient showed us that there was no significant correlation. Obesity (BMI >30) was first recognized by the WHO as a risk factor for serious illness in patients with influenza during the 2009 H1N1 pandemic⁽¹⁹⁾. In a study conducted in Mexico, in which children and adults were examined together, it was observed that both low-weight and morbidly obese patients had influenza more severely than those with normal body weight similar to our study⁽²⁰⁾. It has been demonstrated that during an influenza pandemic in Türkiye, the need for intensive

care increased in the presence of obesity and malnutrition in children⁽¹⁶⁾.

When the relationship between the presenting symptom and viral agent of the patients in the study was examined, muscle pain was more common in patients with influenza B than in those with influenza A and more than one virus. In a systematic review, there was no significant difference between influenza A and B subtypes with other symptoms except myalgia; it has been reported that myalgia is more common in influenza B than in influenza A⁽²¹⁾. Similarly, in many studies evaluating pediatric influenza cases in the literature, children with influenza B infection were found to have higher CK value^(22,23). Although muscle pain was more common in patients with influenza B, no similar relationship was found in terms of CK elevation. Influenza-associated myositis in children is usually mild and regresses within 3-5 days with bed rest and anti-inflammatory drugs⁽²⁾.

The most common complication was pneumonia. One-fourth of these patients required respiratory support during follow-up. In a large series conducted in the United States, it was reported that the most common complication of influenza was respiratory complications, with pneumonia being the most common among them⁽²¹⁾. In our study, oseltamivir was initiated in 63.7% of patients, and antibiotic treatment was initiated in 74.4% of patients due to secondary bacterial infections [most commonly pneumonia (52%)].

The American Society for Infectious Diseases recommends initiating treatment for patients of all ages hospitalized for influenza and its complications and for patients at higher risk for influenza-related complications, regardless of the time of symptom onset⁽²²⁾. It is known that the earlier oseltamivir treatment is initiated in influenza infection, the better the clinical outcomes⁽²³⁾. In a Cochrane analysis, oral oseltamivir and inhaled zanamivir shortened the illness duration by 36 hours in 1255 laboratory-confirmed pediatric patients⁽⁵⁾. In our study, no statistically significant differences were found between the time of initiation of oseltamivir and the rates of complications, need for antibiotics, respiratory support, hospitalization in the service-intensive care unit, and mortality rates.

Influenza, on the other hand, is usually a self-limiting condition in healthy individuals. For this reason, only supportive treatment is applied to individuals without an underlying chronic disease and to those without complications. Antipyretic drugs, adequate fluid intake, and rest are recommended^(1,5). In a sentinel surveillance study

conducted jointly in France and Türkiye, it was emphasized that 26% of laboratory-confirmed influenza cases in France and 55% of cases in Türkiye were prescribed antibiotics, and the rate of unnecessary antibiotic use in influenza cases in both countries was high⁽²⁴⁾. As a result of these findings, physicians should appropriately determine the indication and risk of complications when deciding on the initiation of oseltamivir and antibiotic treatment during influenza.

The American Academy of Pediatrics and the CDC recommend that all children aged 6 months and older without medical contraindications be vaccinated annually for influenza^(25,26). Although most patients in our study had risk factors for severe influenza infection, such as young age, underlying chronic disease, and obesity; vaccination rates were found to be insufficient. According to data from the Global Influenza Hospital Surveillance Network, the rate of influenza vaccination among children under the age of five in Türkiye was 2.1% in the 2015-2016 season and 1.3% in the 2016-2017 season⁽²⁷⁾. It was noticed that the rate of 2.4% in our study was still above the country average. Since our study is a single-centered study, it cannot reflect general data in Türkiye. In addition, the retrospective nature of the study limited the accessibility of the whole data. Only hospitalized patients were included in the study. Therefore, outpatients with mild clinical courses were not included.

Study Limitations

The strength of this study is that it compares a large number of children admitted with microbiologically confirmed. Despite its strengths, our study has several limitations. First, it is a single-centre retrospective study. Its retrospective design and reliance on hospital data may limit generalizability. We only evaluated three influenza season so our findings may not be generalizable. In addition, we would like to follow up our patients to determine whether there have long-term impact of influenza.

Conclusion

Influenza is an important disease, especially in children under the age of two. The incidence of co-infection was also higher in this age group than in older children. Respiratory system complications were the most frequently detected complications in the study population; approximately one-fourth of the patients received respiratory support, and one-fifth received intensive care support. It has been observed that underweight and overweight/obese patients require more intensive care than those with normal body weight.

There were no significant relationships between the time of initiation of oseltamivir treatment and the length of stay in the pediatric service-intensive care unit, antibiotic and respiratory support needs, complications, and mortality rates. In general, the vaccination rate of patients with several risk factors for influenza were very low in our study.

Ethics

Ethics Committee Approval: Prior to the study, permission was obtained from the Ethics Committee of Aydın Adnan Menderes University (number: 48843899-804.01, date: 24.07.2020).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.S.Ö., S.S.K., G.S.Öz., Concept: G.S.Ö., S.S.K., G.S.Öz., Design: G.S.Ö., S.S.K., G.S.Öz., Data Collection or Processing: G.S.Ö., S.S.K., G.S.Öz., Analysis or Interpretation: G.S.Ö., S.S.K., G.S.Öz., Literature Search: G.S.Ö., S.S.K., G.S.Öz., Writing: G.S.Ö., S.S.K., G.S.Öz.

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