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Evaluation of clinical, laboratory and prognosis of patients in an influenza epidemic

Bir influenza epidemisinde hastaların klinik, laboratuvar ve prognozlarının değerlendirilmesi

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Abstract

Purpose: Influenza is an infectious respiratory disease that causes widespread epidemics and pandemics in the community. It is usually self-limiting but may cause significant morbidity and mortality due to complications. We aimed at evaluating the clinical, laboratory and prognosis of adult patients hospitalised with a pre-diagnosis of seasonal influenza.

Materials and methods: It is a descriptive study based on the data from 50 patients hospitalised with a preliminary diagnosis of seasonal influenza between 1 December 2015 and 31 January 2016.

Results: The average age of the patients was 55.44±17.17 years (20-89) and 64% of them were women. Of the cases, 36% were H1N1 positive, 30% were H3N2 positive and 34% had negative PCR results. The time from the onset of symptoms to hospital admission was 3.72±2.51 days (1-11). Comorbidities were present in 38 (76%) patients. Four patients had mortality.

Conclusion: Influenza can be self-limited according to the characteristics of the host, as well as cause mortality. In this study, it was found to cause severe illness and death in a healthy young adult. Therefore, it is important to avoid contact with infected patients, hand washing and vaccination to reduce influenza and its complications. In addition, if our preliminary diagnosis of influenza continues, further evaluations should be made even if the PCR is negative.

Key words: Influenza, epidemic, mortality, H1N1, vaccine.

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Öz

Amaç: İnfluenza, toplumda yaygın olarak görülen epidemi ve pandemilere yol açan bulaşıcı bir solunum yolu hastalığıdır. Genellikle kendi kendini sınırlayabilirken komplikasyonlar nedeniyle önemli morbidite ve mortaliteye neden olabilir. Mevsimsel grip ön tanısıyla yatırılarak takip edilen erişkin hastaların klinik, laboratuvar ve prognozlarının değerlendirilmesi amaçlandı**.**

Gereç ve yöntem: 1 Aralık 2015-31 Ocak 2016 tarihleri arasında mevsimsel influenza ön tanısı ile yatırılan 50 hastanın bilgilerine dayanan tanımlayıcı bir araştırmadır.

Bulgular: Hastaların ortalama yaşı 55,44±17,17 (20-89) ve %64'ü kadın cinsiyette idi. Olguların %36'sı H1N1 pozitif, %30'u H3N2 pozitif ve %34'ünün PCR sonucu ise negatif idi. Semptomların başlamasından itibaren hastaneye başvurana dek geçen süre 3,72±2,51 gündü (1-11). 38 (%76) hastanın komorbiditesi bulunmaktaydı. Dört hastada mortalite ile sonuçlandı.

Sonuç: İnfluenza, konağın özelliğine göre kendi kendi sınırlayabildiği gibi mortaliteye de neden olmaktadır. Bu çalışmada sağlıklı, genç bir erişkinde şiddetli hastalık ve ölüme neden olduğu görüldü. Bu nedenle influenzayı ve komplikasyonlarını azaltmak için enfekte hastalar ile temastan kaçınmak, el yıkama ve aşılama önemlidir. Ayrıca influenza ön tanımız devam ediyorsa PCR negatif olsa bile ileri değerlendirmeler yapılmalıdır.

Anahtar kelimeler: İnfluenza, epidemi, mortalite, H1N1, aşı.

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Introduction

Influenza is a common, highly contagious, acute viral respiratory disease worldwide [1]. Influenza virus is an RNA virus from the Orthomyxoviridae family and is classified in three groups as A, B and C. In recent years, influenza D has also been identified [2]. Influenza A and B are the most common types that cause disease in humans. Influenza C-related acute respiratory disease has been reported in children and is rare in adults [3].

Influenza virus is the causative agent that is prevalent in the community, whose clinic ranges from mild to severe and can cause death. High fever, dry cough, burning in the throat, malaise, generalised muscle and joint pain, headache and, to a lesser extent, nausea, vomiting and diarrhoea are some of the symptoms [4].

H1N1 virus has been identified as a new influenza strain that first emerged in Mexico in 2009 and carries the genes of human, swine and avian influenza viruses [5]. It was announced as the first pandemic of the 21st century by the World Health Organization on 11 June 2009 [6].

In this study, we aimed at evaluating the clinical, laboratory and prognosis of adult patients who were hospitalised with a pre-diagnosis of seasonal influenza in Kutahya Training and Research Hospital between 1 December 2015 and 31 January 2016.

Materials and methods

This is a descriptive study based on the data from patients admitted to the infectious diseases and pulmonology clinics with a preliminary diagnosis of seasonal influenza between 1 December 2015 and 31 January 2016. Nasopharyngeal swabs were taken on special transport medium and sent to the reference laboratory in special transport containers. Diagnosis of the samples was made by real time polymerase chain reaction (RT-PCR). The samples were analyzed by RT-PCR for respiratory viruses such as coronavirus, human bocavirus, parainfluenza type 1-2-3-4, respiratory syncytial virus A and B, rhinovirus, adenovirus, enterovirus, parechovirus, influenza A(H1N1), influenza A(H3N2), influenza B, human metapneumovirus. Those who did not show any of these viruses were considered negative.

The study included patients over 18 years of age. Based on the sample result, the patients were assigned into H1N1, H2N3 and negative groups and evaluated in terms of age, gender, duration of symptoms until admission to the hospital, clinical properties, laboratory tests at diagnosis and follow-up [complete blood count, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, C-Reactive Protein (CRP) etc.], radiologic imaging, treatments, and prognosis.

Information of the patients was retrieved from their medical records and hospital files by retrospective scanning.

The statistical analysis of the data was performed using the Statistical Package for Social Sciences (SPSS) 22.0 statistical package program. Descriptive statistics were expressed as number, percentage, mean, standard deviation, median and interquartile range. Kolmogorow Smirnov and Shapiro Wilk tests were used to evaluate whether the data met the normality hypothesis. Chi-square and Kruskall-Wallis tests were used for the data analysis (since the data did not meet the normality hypothesis). *P* values below 0.05 were considered statistically significant.

The study was approved by the Non-Interventional Clinical Research Ethics Committee of Kutahya Health Sciences University on 11/11/2021 with the decision numbered 2021/15-08.

Results

At the time of admission, patients complained of fever, cough, sputum, sore throat, headache, myalgia, and malaise. Fever, cough, myalgia, and malaise were the most common symptoms. The difference between genders was not statistically significant, although 32 (64%) of the cases were women and 18 (36%) were men ($p>0.05$). Of the cases, 36% were H1N1 positive, 30% were H3N2 positive and 34% had negative PCR results. The distribution of the samples by gender is given (Table 1). The age parameter met the normality hypothesis, whereas the blood leukocyte count, platelet, AST, ALT, LDH and CRP parameters did not. The average age was 55.44±17.17 years [minimum (min):20, maximum (max):89, median: 56.50]. Twenty-six percent of the patients received treatment in

intensive care, 24% in infectious diseases, 22% in pulmonology, 6% in internal medicine and 22% in other units. The time from the onset of symptoms to hospital admission was 3.72±2.51 days (min:1, max:11). An underlying disease was noted in 38 patients (76%), four (8%) had chronic renal failure (CRF), eight (16%) had diabetes mellitus (DM), and ten (20%) had hypertension (HT). Sixteen (32%) patients had chronic obstructive pulmonary disease (COPD), which was the most common comorbidity (Table 2).

Table 1. Nasopharyngeal sample results by gender

	Sample			
Gender	**H1N1 n(%)**	**H3N2 n(%)**	**Negative n(%)**	***p* value**
Female	12 (37.5%)	9 (28.1%)	11 (34.4%)	
Male	6 (33.3%)	6 (33.3%)	6 (33.3%)	>0.05

Table 2. Demographic and laboratory parameters of patients with prediagnosis of influenza

		Mean ± S.D	**Median (IQR**	**Min- max**
Age		55.44±17.17	56.5 (44-64.75)	20-89
Gender (n /%)	Female		32 (64%)	
	Male		18 (36%)	
Sample (n/%)	H1N1		18 (36%)	
	H3N2		15 (30%)	
	Negative		17 (34%)	
Time until hospital admission		3.72±2.51	3 (2-4)	1-11
Underlying disease (n/%)	COPD		16 (32%)	
	None		12 (24%)	
	HT		10 (20%)	
	DM		8 (16%)	
	CRF		4 (8%)	
Inpatient service (n/%)	Chest diseases		11 (22%)	
	Infectious diseases		12 (24%)	
	Internal medicine		3 (6%)	
	Other		11 (22%)	
	Intensive care		13 (26%)	
Blood Leukocyte count (mm3)		8894±4845.13	7350 (5750-11025)	3100-24000
Platelet (mm3)		225260±117713.04	198000 (140000-291000)	99000-657000
AST (IU/L)		68.62±220.89	30 (20-40)	8-1579
ALT (IU/L)		46.96±120.39	20 (15.75-31.25)	6-811
LDH (IU/L)		275.44±271.5	200 (147.25-280)	120-1482
CRP (mg/L)		98.12±77.57	86 (27.75-159)	5-319
Result (n/%)	Discharge		46 (92%)	
	Exitus		4 (8%)	

Abbreviations: S.D: standard deviation, IQR: Interquartile range, min: minimum, max: maximum AST: Aspartate aminotransferase ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, CRP: C-reactive protein, CRF: Chronic Renal Failure COPD: Chronic Obstructive Pulmonary Disease

The laboratory results of patients with a pre-diagnosis of influenza are summarized in Table 2.

Patients with elevated AST and ALT levels were tested for viral hepatitis and the results were negative. Patients with suspected influenza were isolated in the infectious diseases ward. They were trained on hand washing, use of masks, gloves and disinfectants. All suspected cases were treated with oseltamivir for five days and nonspecific antibiotic treatment was given to patients with suspected bacterial superinfection. All of the 50 patients we had inpatient follow-up and treatment had a pneumonia clinic. Pneumonic consolidation or ground glass findings were detected on lung imaging.

Forty-six patients (92%) recovered and were discharged, whereas two patients diagnosed with H1N1 (4%), one patient diagnosed with H3N2 (2%) and one patient with negative results (2%) died. There was no significant difference in the sample results (H1N1, H3N2 and other) between the discharged and deceased patients (p>0.05). One of the H1N1 positive patients who died was a 31-year-old man with no comorbidities and the other was an 89-year-old woman with CRF.

The younger patient was diagnosed with acute tonsillitis in an external center and was hospitalized with nonspecific antibiotic treatment approximately five days before his admission to our hospital. But, as fever persisted and his complaints of cough, shortness of breath and bloody sputum persisted, he was referred to our hospital. He was hospitalized with a pre-diagnosis of pneumonia due to influenza. Laboratory tests revealed WBC: 3300/mm^3, platelet: 116.000/mm^3, AST: 1579 IU/L, ALT: 811 IU/L, LDH: 1482 U/L, CRP: 105 mg/L (<5). Thoracic computed tomography showed bilateral diffuse pneumonic infiltration areas. The patient, who had previously used antibiotics, was started on piperacillin-tazobactam, levofloxacin, teicoplanin and oseltamivir. He was transferred to the intensive care unit on the second day of hospitalization due to low saturation and was followed up. The patient after being intubated one day after admission to the intensive care unit died on the fourth day of hospitalization due to respiratory arrest. Among the deceased patients, the 89-year-old patient also had a pneumonia clinic.

An 81-year-old H3N2 positive woman with CRF and a 54-year-old woman with a negative influenza result were also deceased. The 81-year-old patient complained of respiratory distress and had a pneumonia clinic. She was started on oseltamivir and piperacillin-tazobactam treatment. The patient died on the third day of hospitalization due to respiratory and cardiac arrest. The 54-year-old patient with underlying COPD who was hospitalized with a pre-diagnosis of influenza-associated pneumonia and whose PCR result was negative died on the 15th day of hospitalization. Posteroanterior chest x-ray showed infiltration areas in the right lower and mid lobes.

Discussion

A novel H1N1 virus emerged in 2009 [7]. Seasonal influenza cases are seen every year due to Influenza A (H1N1, H3N2 subtypes) and Influenza B, usually with one subtype being more dominant [8]. Some data have reported that severe influenza infection in prepubertal period is more common in men [9, 10]. In a study conducted in Australia, it was found that the proportion of women to men was low in children under 15 years of age and adults over 75 years of age, but higher between 20-65 years of age [11]. In a study by Saltoglu et al. [12] during the H1N1 pandemic in 2009, the number of women was found to be higher, and although it was similar in our study, it was not statistically significant.

The average age of patients followed up with a diagnosis of influenza was found to be 41.91 (18-82) years in a study of 34 cases and 33 (17-82) years in another study of 84 cases [12, 13]. In a systematic review and meta-analysis study, aging was found to be a risk factor for seasonal influenza [14]. In line with the literature, the oldest patient in our study was 89 years of age and 24% of our patients were over 65 years of age (median age 56.50 years). In addition to the patients who died at an advanced age, a 31-year-old male patient with no known comorbidities had H1N1 virus-associated pneumonia and died due to respiratory failure.

In Spain, 10% of nasopharyngeal samples from intensive care patients with severe respiratory failure had false negative results and it was concluded that a negative RT-PCR result does not exclude H1N1 [15]. In

critically ill patients with lower respiratory tract disease, there may be influenza viral clearance in the upper respiratory tract, so molecular testing of lower respiratory tract specimens is recommended to detect the virus [16]. When the virus reaches the lower respiratory tract, the probability of detecting the agent in nasopharyngeal specimens decreases. In line with this information, the patient with a negative influenza PCR result being admitted to the hospital five days after the onset of symptoms may have had a negative effect on the PCR result. In addition, a negative PCR result despite testing for other viruses causing respiratory tract infections other than influenza suggests that there may have been false negativity due to sample collection or transport errors.

In influenza, the virus starts to spread one day before the onset of symptoms and continues for up to seven days. This period may be prolonged in children, the elderly and immunocompromised patients. In the study of Yasar et al. [17] the time from the onset of symptoms to hospital admission was found to be 3 days. During the season of influenza between December 2015 and April 2016, the duration was found to be 2 days in 132 cases evaluated in the paediatric age group [18]. Similarly, the mean duration in this study was 3.72±2.51 days (min:1, max:11).

A study found that H1N1 positivity was 57%, H3N2 positivity was 2%, and Influenza B positivity was 40.4% in samples taken from hospitalized patients [19]. The CDC reported that 70.8% were influenza A and 29.2% were influenza B according to the United States of America (USA) influenza surveillance data from the 2015-2016 season. Subtyping was reported as 80.7% H1N1 and 19.3% H3N2 for influenza A; 68.5% B/Yamagata and 31.5% B/Victoria for influenza B [20]. In another study during the same influenza season, an analysis of the subtypes of 234 Influenza A cases revealed that the dominant type was H1N1 with a rate of 94.9% and the rate of H3N2 was 5.1% [21]. In the present study, the rates were close to each other with H1N1 positivity at 36% and H3N2 positivity at 30%; influenza PCR results were negative in 34% of the samples and influenza B was not detected.

The presence of comorbidities increases the risk of serious illness. The disease was more severe in patients with chronic lung disease, pregnancy, and obesity [22]. In New York, of the 47 cases who died due to H1N1, 79% were found to have underlying diseases and risk conditions [23]. In the present study, risk factors for mortality were not investigated, but the 31-year-old case with mortality had no comorbidities, which is controversial with this information. There are studies describing that elderly patients may have cross-reactive antibodies that protect against H1N1 due to exposure to influenza infection from an early age and a history of influenza vaccination [24, 25]. According to this study, this may have been due to the lack of sufficient protective antibodies in our patient who died at a young age or the presence of another factor that could not be identified. The other patients who died had underlying diseases such as CRF and COPD.

Empirical antiviral treatment should be considered in patients with a pre-diagnosis of seasonal influenza in the absence of comorbidities and in the younger age group, and treatment can be adjusted, if necessary, upon further evaluation. Patients with underlying diseases should be informed about influenza, vaccinated, and should be admitted to hospital as soon as possible when symptoms occur.

The limitations of this study are the small number of patients, as it was a single-center, retrospective study and did not include outpatients. We aimed to draw attention with the conclusion of our study, but multicenter studies with large patient coverage are warranted to generalize this conclusion.

In conclusion, other than the patients who died at an advanced age, mortality was also reported in a young patient without comorbidities. H1N1 can also cause severe illness and death in healthy young adults. As in our study, RT-PCR negativity in nasopharyngeal samples is not conclusive evidence to exclude influenza. False negativity should be kept in mind. If our strong pre-diagnosis of influenza continues, we should perform further examinations and evaluations. The best way to prevent influenza and influenza-related complications is to be vaccinated annually, morbidity and mortality can be reduced by vaccination. Avoiding contact with infected patients and hand washing are important in protection against influenza other than vaccination, training on this issue should be increased.

Conflict of interest: The authors declare that there is no conflict of interest.

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Authors' contributions to the manuscript

The study conception was planned by T.T. and D.M.O. Patient data were provided by T.T., D.M.O., S.E.P., and A.B.U. edited the materials and methods section. T.T. and A.B.U. performed the analysis and interpretation of the study. Writing was done by T.T, D.M.O, S.E.P., A.B.U. reviewed and made corrections. All authors read, discussed, and approved the final version of the manuscript.