J Surg Med. 2019;3(1):8-12.
DOI: 10.28982/josam.437319

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN: 2602-2079

Clinical and demographic characteristics of influenza B outbreak in Erzincan province of Turkey

Tükiye, Erzincan ilinde influenza B salgınının klinik ve demografik özellikleri

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Ethics Committee Approval: The study was approved by the Ethics Committee of Erzincan University (Approval no: 20.06.2017-9/5).
Etik Kurul Onayı: Çalışma Erzincan Üniversitesi Etik Kurulu tarafından onaylandı (Onay no: 20.06.2017-9 / 5).

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Received / Geliş Tarihi: 26.06.2018
Accepted / Kabul Tarihi: 16.07.2018
Published / Yayın Tarihi: 28.07.2018

Abstract

Aim: Seasonal epidemics of influenza are responsible for significant morbidity and mortality worldwide. We aimed to investigate distribution of seasonal influenza viruses, and clinical and demographic characteristics of influenza B epidemics in Erzincan province of Turkey.

Methods: A total of 103 patients who presented to our hospital in spring the season in accordance with influenza case management schema in line with the recommendations by the World Health Organization and Ministry of Health were included in this study. Cepheid SmartCycler system, which is an integrated RNA replication and detection device based on microprocessor controlled I-CORE® (Intelligent Cooling / Heating Optical Reaction) module was used in order to detect Influenza A / Influenza B viruses.

Results: Influenza was positive in 28 (27.1%) of all patients who presented with suspected Influenza, with 23 (22.3%) being Influenza B and 5 (4.9%) Influenza A. Of patients with positive Influenza B, 18 (78%) had one or more chronic diseases. Of the patients, 15 (65%) were diagnosed with one of the chronic pulmonary disease, 8 (35%) one of the chronic cardiac diseases, and 3 (13%) diabetes mellitus. Leukopenia and thrombocytopenia were more common than leucocytosis. Seven patients were followed-up as inpatients. At the follow-up period, three of the patients were taken to the intensive care unit and 2 of them died. Whereas the remaining patients were discharged with recovery.

Conclusion: We observed that, Influenza B progressed more seriously than we expected. For this reason, we think that immunity level of the community against Influenza B should be raised with vaccination campaigns involving different subtypes of Influenza B.

Keywords: Influenza, Influenza B virus, Epidemics, Seasonal epidemics, PCR

Öz

Amaç: Mevsimsel influenza epidemileri, dünya çapında önemli morbidite ve mortalite nedenidir. Çalışmamızda Türkiye'nin Erzincan ilinde mevsimsel influenza virüslerinin dağılımı ile influenza B salgınının klinik ve demografik özelliklerinin araştırılması amaçlanmıştır.

Yöntemler: 2017 bahar döneminde Dünya Sağlık Örgütü ve Sağlık Bakanlığı'nın önerileri doğrultusunda influenza vaka yönetim şemasına uygun olarak, hastanemize başvuran 103 hasta çalışmaya dahil edildi. Özel eküvyon çubukları yardımıyla nazofarengeal sürüntü örnekleri alındı. Influenza A / Influenza B virüslerini tespit etmek için mikroişlemci kontrollü I-CORE® (Akıllı Soğutma / Isıtma Optik Reaksiyonu) modülünü temel alan entegre bir RNA çoğaltma ve algılama cihazı olan Cepheid SmartCycler Sistemi kullanıldı.

Bulgular: İnfluenza ön tanısı ile başvuran tüm hastaların 28 (%27,1)'i influenza pozitif bulunurken, 23 (%22,3)'ü Influenza B, 5 (% 4,9)'i Influenza A saptandı. Influenza B pozitif saptanan hastaların 18 (%78)'i bir veya daha fazla kronik hastalığa sahip olduğu saptandı. Hastaların 15 (%65)'i kronik akciğer hastalıklarından birine, 8 (%35)'i kronik kalp hastalıklarından birine, 3 (%13)'ü diabetes mellitus tanısı alan kişilerdi. Influenza B pozitif hastalarında en sık karşılaştığımız semptomlar; myalji, öksürük, ateş ve nefes darlığıydı. Lökopeni ve trombositopeni, lökositozdan daha sık saptandı. Hastaların 7'si yatırılarak takip edildi. Takip edilen dönemde hastaların 3'ü yoğun bakım servisine alındı, bu hastaların 2'si öldü. Diğer hastalar ise şifa ile taburcu edildi.

Sonuç: İnfluenza B'nin beklediğimizden daha ciddi seyrettiğini gözlemledik. Bu nedenle, İnfluenza B'ye karşı topluluğun bağışıklık düzeyinin, farklı tipte İnfluenza B alt tiplerini içeren aşılama kampanyalarıyla artırılması gerektiğini düşünüyoruz.

Anahtar kelimeler: İnfluenza, İnfluenza B virüsü, Epidemiler, Mevsimsel epidemiler, PCR

How to cite / Atıf için: Ünver E, Çıkman A, Karakeçili F. Clinical and demographic characteristics of influenza B outbreak in Erzincan province of Turkey. J Surg Med. 2019;3(1):8-12.

Introduction

Influenza viruses from the orthomyxovirus familia have negative-polarity, single-chain, enveloped and segmented RNA [1,2]. These viruses are divided into three types as A, B and C. Recently, Influenza D virus which has been proven to cause illness in human as the fourth type has been described [3,4].

Influenza A (IA) and Influenza B (IB) types lead to high rates of morbidity and mortality in humans during yearly seasonal epidemics [5,6]. IA is a virus with pandemic potential, because it is an animal shelter. Especially migratory birds and pigs play an important role in the formation of subtypes again through viral mutation [7].

Since antigenic drift of IB is slower, these viruses do not lead to antigenic drift. Thus, IB is not expected to cause a pandemic [8]. However, especially since the 1980s, IB viruses have become widespread due to globalization and intense travels in recent years. From these years, phylogenetically two different subtypes of IB (B / Yamagata and B / Victoria) have emerged as a global problem [9]. Because these IB subtypes have become widespread, the World Health Organization (WHO) recommended to include these phylogenetic influenza subtypes to the influenza vaccines from 2012/13 influenza session [10].

Unlike the intensely investigated IA viruses, IB viruses have drawn a relatively less interest [11]. However, IB viruses are among the most important causes of morbidity and mortality in human population [12]. A complete understanding of the epidemiological, clinical, and biological features of IB is important in order to better control of this crucial pathogen.

Recently, IB has gain importance and commonly reported worldwide. Data about the incidence, disease burden and circulatory pathways of IB in Turkey are limited. In this study, we aimed to investigate distribution of seasonal influenza viruses, and clinical and demographic characteristics of influenza B epidemics in Erzincan province of Turkey.

Materials and methods

Patients and samples

A total of 103 patients who presented to our hospital between 01 March 2017 and 07 June 2017 in accordance with influenza case management schema in line with the recommendations by the World Health Organization (WHO) were included in this study [13]. Accordingly; patients with a fever of 38 ^{o}C which cannot be explained with other reasons or a history of fever together with at least one of the complaints of diffuse body pain, sore throat, headache, nasal discharge, cough, and shortness of breathing were accepted as an Influenza case. Whereas the persons aged under 2 years, above 65 years, and those with immunosuppression were considered as possible cases in the presence of fever. Shortness of breath or respiratory distress, changes in vital signs, hypoxia, changes in consciousness, severe dehydration, and bronchopneumonia or pneumonia on chest X-ray were considered as the indications for hospitalization. In accordance with the instruction by the WHO; patients younger than 2 years old and those with chronic pulmonary, cardiovascular, renal, hepatic, hematologic, metabolic, and neuromuscular disorders, and immunosuppression status were accepted as the patients at risk. Whereas the patients who did not fall into any of these groups were considered as health hosts.

All patients' age, gender, complaints and physical examination findings were recorded. As routine examinations; peripheral smear, levels of electrolytes, C-reactive protein (CRP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), creatine phosphokinase (CK) and plasma creatinine were studied. Blood cultures were performed and postero-anterior chest X-rays were ordered at the admission and during follow-up of the patients with persistent fever.

Nasopharyngeal swab samples were collected from all patients. After the Nasopharyngeal swab samples were taken through swab rods, they were put into a viral transport medium (HiViral Transport Kit, India), and quickly sent to the laboratory following cold chain and biosafety rules in an appropriate carrier container without waiting.

Laboratory diagnosis

IA and IB viruses were studied in the samples that were sent to the laboratory, after appropriate preparation procedures. The laboratory analyses were performed using SolMag®12 Full Automated Nucleic Acid Isolation System and SolMag® Virus Nucleic Acid Isolation Kit (Taiwan R.O.C). In this system; first the sample was diluted with 1200 µl RNA Carrier free water. 20 µl of Carrier was pipetted into the sample tube. Sample of 480 µl was added on it. Reactive cartridges and pipette tips were respectively inserted. The samples were placed in the 'S' section of the sample rack, the Elution tube in the 'E' region, and the internal control in the 'IC' region. The study was then initiated in line with the recommendations by the manufacturer. 100 µl RNA was isolated as a result of the nucleic acid purification protocol, which took about 45 minutes.

Cepheid SmartCycler system, which is an integrated RNA replication and detection device based on microprocessor controlled I-CORE® (Intelligent Cooling / Heating Optical Reaction) module was used in order to detect Influenza A / Influenza B viruses. RealCycler FLURSV (Progenie Molecular, Spain), which enables real time PCR qualitative determination of RNA from IA and IB viruses simultaneously was used in the clinical samples. These study kits targeted M1 and M2 genes that are conservative gene regions of pathogen microorganisms. Whereas amplifications were assessed using SmartCycler II thermocycler (Cepheid). According to the instructions by the manufacturer, a master mixture of 23 µl was prepared, DNA samples of 2 µl were added and a total reaction volume of 25 µl was studied. The data were analyzed with SmartCycler system software using absolute quantification-adaptation point analysis method.

Ethical considerations

The study was approved by the Ethics Committee of Erzincan University (Approval No: 20.06.2017-9/5). Written informed consent was obtained from all participants. All participants were informed through "Informed Consent Form" and gave consent for the study. The relevant forms were received from the participants over 18 years old by themselves, and from the parents of the participants aged under 18 years.

Statistical analysis

Statistical evaluation of the data was carried out using Statistical Package for Social Sciences for Windows version 18.0 (SPSS, Chicago, IL, USA) software. Normality of the variables was analyzed using Kolmogorov-Smirnov test. The descriptive statistics are given as median and minimum-maximum values for the non-normally distributed variables. Mann-Whitney U tests was used in order to evaluate the variables with a disrupted distribution. Group comparisons were made with Chi-square test. P values less than 0.05 were considered statistically significant.

Results

In the study period; 59 of the patients were referred to the department of chest diseases, 26 to the pediatric diseases, 16 to the infectious diseases and 2 to the other outpatient clinics of our hospital. Influenza was positive in 27.1% (28/103) of all patients who presented with suspected Influenza, with 22.3% (23/103) being Influenza B and 4.9 (5/103) Influenza A. Of the IB positive patients, 10 (43%) were male and 13 (57%) were female with a mean age of 55 years and age range of 1-76 years.

All the patients with IA were identified in March when we began to this study. Whereas patients with IB were identified within a period of about 2 months between 13 March and 05 May (Figure 1). This duration correspondences to the spring season for our study area. In our study, we found that ending of IA endemic and beginning of IB endemic were at about the same dates.

Eighteen of the patients with positive IB were found to have one or more chronic diseases, when influenza B positive and influenza B negative patients were compared. Fifteen of these patients had one of the chronic pulmonary diseases such as asthma or chronic obstructive pulmonary disease, and this value was statistically significant ($p<0.001$). In addition, 8 patients had been diagnosed with one of the cardiac diseases (six hypertension), and this value was statistically significant ($p<0.05$). Three patients had been diagnosed with diabetes mellitus (DM), but these diseases were not found to be significant. Whereas, 5 patients had no any accompanying disease (Table 1).

The most common symptoms in Influenza B patients included myalgia, cough, fever and shortness of breath. Myalgia, cough, fever, headache, nasal discharge and sore throat were statistically significant ($p<0.05$), when influenza B positive and influenza B negative patients were compared. IB positive patients had no any gastrointestinal complaints such as abdominal pain, nausea, vomiting and diarrhea. Symptoms and incidences of the positive patients are presented in Table 1.

When laboratory findings were examined; increased CRP was found in 18, leukopenia in eight, thrombocytopenia in six and leukocytosis in three of the patients with positive IB. Leukopenia and thrombocytopenia were more common findings than leukocytosis. However, none of the laboratory findings was statistically significant.

All the patients referred to the hospital, were studied for IA and IB with PCR on the day of admission. Thus, all of the patients with positive outcome were diagnosed with IA or IB within the day of admission to the hospital. Oseltamivir therapy was initiated in the patients diagnosed with Influenza, on the same day. Seven patients were followed-up as inpatients. At the follow-up period, three of the patients were taken to the intensive care unit and 2 of them died. Whereas the remaining patients were discharged with recovery.

Table 1: Clinical and Demographic Characteristics of Influenza B positive and Influenza B negative patients

Clinical and demographic characteristics	Patient groups [a] Positive (n:23)	Negative (n:75)	p
Gender			
Woman	13 (%57)	30 (%40)	>0.05
Male	10 (%43)	45 (%60)	
Age (year)	55 (1-76)	39 (0-82)	0.008
symptoms			
Myalgia	21 (%91)	4 (%5)	<0.001
Cough	20 (%87)	35 (%47)	0.001
Fever	19 (%83)	24 (%32)	<0.001
Shortness of breath	13 (%56)	26 (%35)	>0.05
Headache	8 (%35)	2 (%3)	<0.001
Nasal discharge	8 (%35)	6 (%8)	0.004
Throat ache	6 (%26)	2 (%3)	0.002
Sputum	3 (%13)	15 (%20)	>0.05
Laboratory Findings			
CRP increase	18 (%78)	55 (%73)	>0.05
Leukopenia (<4.000 / mm3)	7 (%30)	9 (%12)	0.05
AST / ALT increase (>40 U / L)	8 (%35)	34 (%45)	>0.05
Thrombocytopenia (<150.000 / mm3)	5 (%22)	7 (%9)	>0.05
Increase in creatinine (>1.09 mg / dL)	5 (%22)	15 (%20)	>0.05
Leukocytosis (>10,000 / mm3)	3 (%13)	18 (%24)	>0.05
Chronic disease			
Chronic lung disease	15 (%65)	17 (%23)	<0.001
Chronic heart disease	8 (%35)	10 (%13)	<0.05
Diabetes mellitus	3 (%13)	6 (%8)	>0.05
Inpatient	7 (%30)	30 (%40)	>0.05
ICU Inpatient	3	0	-
Death	2	0	-

[a] Influenza B positive patients and Influenza B negative, n: Number of patients

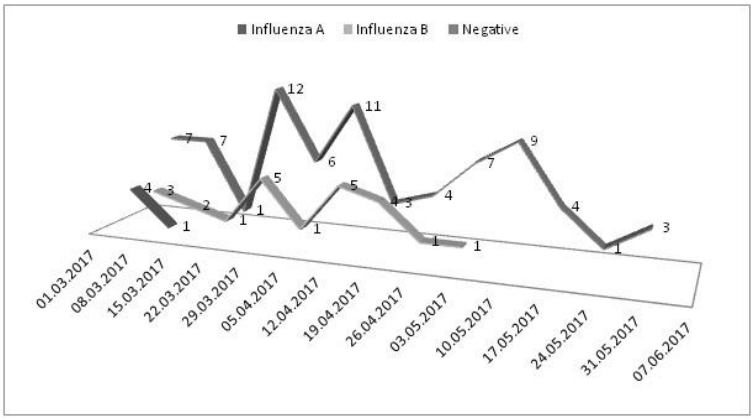

Figure 1: Distribution of the patients with positive IB by time period

Discussion

Seasonal influenza causes 3 to 5 million severe illnesses and 250,000 to 500,000 human deaths worldwide each year [14]. Traditionally, it is believed that IA accounts for majority of seasonal influenza cases [15]. However, IB constitutes an important part of seasonal influenza cases out of the periods of pandemics by IA [16].

Recent studies report significant increases in IB infections. The incidence of IB has been reported as 23.9% in a study from Spain, conducted between 2010 and 2016 [17]. There are several studies demonstrating that IB is more dominant in some periods in the epidemiology of seasonal influenza. Australian Influenza Surveillance Report stated that IB was the dominant type of Influenza in 2015 in Australia. According to the Australian Influenza Surveillance Report for January-October period; 61% of the cases were found as IB, and 38% IA (29% A (subtype unclear), 7% A (H3N2) and 2% A (H1N1) pdm09) [18]. In another study, Radovanov et al. [19] found that influenza

activity in the winter season in Vojvodina region increased over January and February months and peaked at the end of February, and that 53.4% of the positive cases were IB and 43.6% IA.

Weekly influenza surveillance reports are published in many countries worldwide due to several reasons such as tracking influenza viruses, predicting the possible epidemics, determination of the subtypes of influenza viruses, evaluation of severe influenza cases and identification of the high-risk groups in terms of the severity of diseases and mortality. Within this framework; especially WHO regularly publishes Influenza Surveillance Reports. When laboratory data of the WHO GISRS (Global Influenza Surveillance and Response System) were examined; the incidence of IA was found between 77.3% and 34.7%, and the incidence of IB between 65.3% and 22.7% in the period of 20 February – 14 May 2017. Whereas, IB type was reported to be more commonly encountered from the beginning of April through end of May [20].

In Turkey, Influenza Surveillance Reports are published by the Turkey Public Health Agency of Department of Infectious Diseases. Looking at the 2017 Weekly Influenza Surveillance Reports, IB type is seen to be more dominant in the period matching with our study. When the incidence of influenza viruses were examined over two months from the 12th week to the 18th week in 2017, IB virus has been reported to be more common than IA virus [21]. Our study covers approximately the same period. Similarly to the Turkey data, in our study IB virus was found to be the dominant type in our study area.

Influenza viruses may lead to pandemic in all seasons, particularly in winter [22,23). Influenza season typically starts at the beginning of October, peaks in January and February, and slightly raises at the end of March in the northern hemisphere where also cover our study area [24). Whereas IB usually leads to endemics in summer period and is encountered as the dominant type of influenza viruses [25,26]. Whereas in our study, majority of the cases were identified in March and April that fall into spring period.

Studies have reported similar rates of female and male patients with influenza infections. Although, there are studies with a larger number of female or male patients, none of these studies find a statistically significant difference between the genders [27]. No significant difference was found between the genders in the present study.

Influenza infections are seen in all age groups [15]. Some studies have reported that, children aged under 5 years and elderly people aged over 65 years are more frequently. Although IA and IB were investigated in 26 persons aged under 15 years who were considered as possible cases in line with the recommendations by the WHO and the Ministry of Health, only one child was found to have positive IB. Despite we had patients considered as possible cases in all age groups, the mean age was found as 55 years in our patients with IB, and this value was statistically significant (p=0.008). According to our data, we can say that IB cases were more common among the middle to advanced age group.

Clinical findings of influenza virus are variable and often progress with sudden-onset fever, headache, myalgia accompanied by cough and sore throat [28,29]. Higher fever, increased lymph gland growth, more common gastrointestinal system involvement, and less respiratory system findings may be observed in children than adults, because they previously have not encountered with the virus [30,31]. In our study; myalgia, cough, shortness of breath and fever were found in majority of the patients. There are studies reporting that, abdominal pain and complaints of gastrointestinal systems are more common during IB infections [31]. However, none of the patients with IB positive had complaints of gastrointestinal system. This may be related to the small number of our patients.

The incidence of chronic diseases has been found as high in patients who suffer from influenza. Studies have reported these diseases as particularly asthma, and chronic obstructive pulmonary disease, chronic cardiac diseases and diabetes mellitus [33,34]. In our study, 18 (78%) of the patients with IB had at least one chronic disease. Fifteen of our patients had chronic pulmonary diseases (13 asthma), eight chronic cardiac diseases (6 hypertension) and three DM. Chronic pulmonary diseases and chronic cardiac diseases were statistically significant in the IB positive group.

Until recently, it was thought that IA is more serious. However, some recent studies have shown that IB may progress at least as serious as IA [11,35]. Some studies have reported that IB may lead to serious outcomes especially in children and young adults [36]. Tran et al. [30] reported higher rates of mortality related to pediatric IB infections than IA. Whereas, some studies suggested that the most common type of influenza related with complications and mortality in elderly persons is IA/H3N2 followed by influenza B [36]. Whereas, in our study seven patients were followed-up on inpatient basis, three were taken to the intensive care unit and two of them died. Despite our patients were diagnosed with PCR at the day of admission and treatment was initiated, the rate of mortality was higher than we expected. However, this data should be supported by further studies with a larger number of cases.

The present study has some limitations. Referrals to the hospital were carried out in accordance with the influenza case management schema, and accordingly limited number of patients was enrolled to the study. In addition, other limitations may include that subtypes of Influenza A and B could not be determined, and the study reflects only a certain period of time.

In conclusion, we found that the community in Erzincan is sensitive to IB. This indicates that new and larger pandemics are inevitable in each seasonal influenza period. Immune memory of the community for IB should be improved. In this study, we found that IB can get ahead of IA in different periods of the year and in different regions, and even may be seen at a quite high rate. Therefore, we think that consideration of IB in the epidemiology of seasonal influenza is important. We recommend that, immunization level of the society should be raised with vaccination campaigns including different subtypes of IB, according to the needs of each country.

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