Comparison of clinical, serological, and radiological findings among hospitalized A-H1N1, B-H1N1, and H3N2 influenza patients

Kiana Shirani[1], Seyed Ali Hosseini[2], Behrooz Ataei[1], Alireza Ayatolahi[3], and Shoeleh Yaghoubi[2]

[1]Isfahan University of Medical Sciences
[2]Shiraz University of Medical Sciences
[3]Shahid Sadoughi University of Medical Sciences and Health Services

November 24, 2020

Abstract

Background: Despite remarkable developments in medical science, viral infections still remain serious threats to the global health system. Methods: In this cross-sectional study, we retrospectively compared the clinical, serological, and radiological findings in subjects with confirmed A-H1N1, B- H1N1, or A-H3N2 virus infection. The investigation included data on influenza patients who were admitted to the Al-Zahra Hospital, Isfahan, Iran, from September 2017 to February 2018. Results and Conclusions: Based on statistical analysis, fever was present as the most common clinical manifestation in patients with the three subtypes of influenza. Notably, the fever temperature was much higher among A-H3N2 subjects than A-H1N1 and B-H1N1 subjects ($P<0.05$). The A-H3N2 patients also had significantly higher C-reactive protein (CRP) levels than the other two groups of influenza patients ($P<0.05$). In the chest computed tomography scans, patchy infiltration and middle lobe involvement were found more commonly among A-H3N2 patients ($P=0.012$ and $P=0.021$, respectively) than patients of the other two influenza subtypes. Our clinical observations, serological examinations, and radiological findings are likely to be beneficial in managing patients with influenza and determining the need for further interventions.

Introduction

The influenza virus remains a serious threat to the global health system given the occurrence of three to five million severe cases per year and the high number of mortalities, particularly during pandemics[1,2]. This virus gives rise to a disease with manifestations that are common to some other infections, such as fever, malaise, and headache [3,4]. Three types of influenza viruses affect humans: A, B, and C [5]. Based on the alterations in the hemagglutinin and neuraminidase surface proteins, the type A influenza virus is divided into numerous subtypes. The H3N2 and H1N1 subtypes of influenza A have received considerable attention in recent years. A critical issue that gives rise to major challenges is the mutations that occur in the various influenza virus strains, particularly in the A-H3N2 and A-H1N1 subtypes and the B type[6-8].

In the clinic, it is usually impossible to differentiate infection triggered by various types and subtypes of influenza according to the clinical manifestations [9,10]. Fever is the most commonly reported sign that presents in more than 90% of patients[11,12]. Respiratory complications, gastrointestinal involvement, cardiovascular involvement, and constitutional complaints (e.g., myalgia, malaise, and fatigue) are some of the other signs and symptoms of influenza virus infection (10). The radiological characteristics of subjects with various types of influenza, especially the 2009 H1N1 strain, have been reported in the previous surveys, where differences between patients of mild and severe disease have been discussed. The main findings obtained

from radiological investigations on influenza subjects are ground-glass opacities, areas of consolidation, or a mixed pattern of these two findings (11, 12). In this cross-sectional study, we retrospectively evaluated the thoracic CT findings, serological biomarkers, and clinical features in cases with confirmed A-H1N1, B-H1N1, and A-H3N2 virus infection.

Methods

Patients

The protocol of this cross-sectional study was approved by the Infectious Diseases and Tropical Medicine Research Center of Isfahan University of Medical Sciences (MUI), Isfahan, Iran. Data collection was performed from all consecutive subjects admitted to the Department of Infectious Diseases and Tropical Medicine, Al-Zahra Hospital, MUI, Isfahan, Iran. Our investigation was conducted from September 2017 to February 2018. The criteria for the diagnosis of influenza were based on the U.S. Centers for Disease Control and Prevention (CDC) and included fever (37.8°C or higher), cough, sore throat, runny or stuffy nose, muscle or body aches, headache, tiredness, vomiting, diarrhea, etc. The demographic characteristics of the patients were recorded in a special form. Associated factors including vaccination, contact with birds, recent travel, and contact with patients were also noted.

Virological examination

For virological examination, in all suspected patients, throat swabs were tested for the presence of specific viral antigens for A-H1N1, B-H1N1, and A-H3N2 by means of real-time reverse transcriptase-polymerase chain reaction (RT-PCR). The respiratory samples were sent to the Tehran National Influenza Center in a viral transport medium (Virocult, Medical Wire & Equipment, UK), where the real-time RT-PCR protocol was applied using reagents supplied by the World Health Organization (WHO).

Imaging procedures

In the present study, the chest computerized tomography (CT) scan with intravenous (IV) contrast was performed to examine the pulmonary involvement of the three mentioned viral strains in patients with influenza. In this procedure, 120 ml (350 mg/ml) of IV iohexol (Omnipaque; General Electric) was administered, with images being obtained after a 90-s delay. Provided chest scans were assessed for the presence or absence of patchy infiltration, interstitial infiltration, pleural effusion with or without infiltration, and also the site of lung involvement.

Serological and clinical examination

The assessed clinical manifestations included fever, headache, digestive involvement, myalgia, vocal hoarseness, calf pain, and tachycardia. Each variable was investigated as a simple 'yes or no' for symptoms. We also recorded the white blood cell (WBC), lymphocyte, neutrophil, platelet, C-reactive protein (CRP), alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), blood urea nitrogen (BUN), hemoglobin (Hb), uric acid, lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), creatinine phosphokinase (CPK), total bilirubin (Bil-T), and direct bilirubin (Bil-D) levels; each variable was assessed as a numerical value.

Statistical analysis

Statistical analysis was performed using the SPSS statistical package program, version 22.0 (SPSS, RRID:SCR_002865). The demographic data of the patients were analyzed using the Chi-squared and

Kruskal–Wallis tests. The comparison between the clinical and serological features of subjects with various types of influenza was made using the Chi-squared test. Continuous variables were assessed by analysis of variance (ANOVA) to identify differences between groups. Differences were evaluated further using Scheffe's posthoc test if the ANOVA indicated significance. P-values less than 0.05 were accepted as meaningful differences.

Results

The patients (n=41) were distributed to the three defined groups of infection: influenza A-H1N1 (n=27), influenza B-H1N1 (n=10), and influenza A-H3N2 (n=4). The mean ages in the three influenza groups were 45.7 +- 14.7, 50 +- 15.03, and 46.6 +- 26.65, respectively. There was no significant difference in mean age between the three groups of influenza subjects (P=0.7). However, the mean age of B-H1N1 patients was slightly higher than that of the influenza A-H1N1 and A-H3N2 patients. Overall, 53.7% (22/41) of the patients were male and 46.3% (19/41) were female. There was no meaningful difference in sex between the three groups of patients (P=0.2). The demographic and clinical information of the subjects is summarized in Table 1.

Based on statistical analysis performed on the serological and clinical manifestations, fever was present in most patients with the various types of influenza, with no significant difference in its rate of presence between the three groups (P=0.58). However, as a considerable finding, the fever temperature was much higher in A-H3N2 subjects (38.9 +- 0.18 degC) than in A-H1N1 (38.18 +- 0.29 degC) and B-H1N1 (38.21 +- 0.26 degC) subjects (P<0.05).

Also, we found a significant difference in the levels of CRP between the three groups of influenza patients (P=0.03). However, no meaningful differences were identified in the WBC count or other serological parameters under study (P>0.05). The serological results of the patients are summarized in Table 2.

In the chest CT scans, patchy infiltration and middle lobe involvement were two parameters that had significantly different rates of occurrence between the three types of influenza strains (P=0.012 and P=0.021, respectively) (Figure 1). The findings seen on all chest CT scans included in this study are summarized in Table 3.

Discussion

Influenza can cause signs and symptoms that are indistinguishable from some severe cases of the seasonal common cold. In general, a chest X-ray is the first paraclinical test that is performed for the assessment of respiratory involvement in patients with influenza. In the conditions that the chest X-ray shows the presence of questionable findings of respiratory involvement, a chest CT is requested. Also, it has been suggested that the chest CT is useful in evaluating complications or evidence of mixed infection, but this issue is open to discussion. So far, some studies have investigated the radiological features of influenza patients, especially in A-H1N1 cases. Marchiori et al. (2011) described the high-resolution CT features of fatal cases of influenza A-H1N1 virus-associated pneumonia [13]. The predominant findings included areas of airspace consolidation and ground-glass opacities. Nicolini and co-workers (2011) reported unilateral or bilateral multifocal ground-glass opacities as the predominant feature in chest CTs obtained from influenza patients [14]. In another study performed by Agarwal et al. (2009), patchy consolidations in the lower and central lung zones were reported as the main characteristic of A-H1N1 subjects [15]. Also, Ajlan et al. (2009) stated that unilateral or bilateral ground-glass opacities with or without associated focal or multifocal areas of consolidation are the crucial parameters that should be considered in influenza patients [16].

In our study, the rate of patchy infiltration detection, as a crucial parameter, was significantly different between the three types of investigated influenza strains (P<0.05). Patchy infiltration is considered as a

poorly defined area of lung consolidation with scattered opacification seen on chest imaging. This clinical characteristic has been reported in many studies performed on the influenza disease. Rostami et al. (2011) studied the radiological characteristics of influenza A-H1N1 patients [17]. In their survey performed in the Isfahan city of Iran, patchy infiltration was one of the most common thoracic CT findings in pandemic H1N1. The results of the present study are in agreement with the results of Rostami's study. In another study, Elicker and co-workers (2010) reported the thoracic CT findings of novel influenza A-H1N1 infection in immunocompromised patients [18]. In their study, some patients had atypical CT findings including focal lobar consolidation and patchy lower lobe consolidation with soft tissue centrilobular nodules. Such atypical findings may be indicative of a compromised immune status.

To date, a number of studies have reported the clinical features of various types of influenza, especially the A-H1N1 subtype. Walsh et al. (2002) described the clinical features of influenza-A infection in older hospitalized subjects [19]. They stated that the presence of cough, fever, and severe illness are valuable in opting for respiratory isolation and designing antiviral trials for influenza patients. In 2009, Cao and co-workers listed the clinical features of influenza A-H1N1 patients [20]. Based on their report, the most common symptoms of A-H1N1 influenza patients were fever and cough, which occurred in 67.4% and 69.5% of cases, respectively. In another survey, Hu et al. (2003) surveyed the clinical features of influenza A and B in younger patients and its association with myositis[21]. These researchers reported fever, cough, and rhinorrhea as the most common clinical manifestations, with benign acute childhood myositis being present in 5.5% and 33.9% of the type A and B patients, respectively. Irving and his colleagues (2011) conducted a study for the comparison of clinical manifestations of medically attended influenza-A and influenza-B in defined subjects over four seasons [10]. They concluded that over four influenza seasons, clinical signs and symptoms were alike for cases with predominantly outpatient-attended influenza-A and influenza-B virus infections.

As previously mentioned, fever seems to be the most common influenza manifestation; Calitri et al. (2010), in their cross-sectional study, confirmed this among 2009 H1N1 influenza patients [22]. In another study, Plessa et al. (2010) declared that fever was the most common symptom in pediatric patients with H1N1 influenza[23]. In our cross-sectional study, fever was present in most patients with various types of influenza. Notably, the fever temperature was significantly higher among influenza A-H3N2 subjects than A-H1N1 and B-H1N1 subjects ($P<0.05$). Kaji and co-workers (2003) investigated the differences in clinical features between A-H3N2, A-H1N1, and B influenza subjects in Japan [24]. They reported that A-H3N2 influenza was more severe than A-H1N1 or B in terms of fever, leukopenia, and CRP level elevation. Our finding related to fever is in agreement with the Kaji et al. study.

Dynamic determination of inflammatory agents may offer important insights into individual alterations in the control of inflammation and risk for disorders. The CRP is produced by the liver in response to signaling by pro-inflammatory cytokines. A high level of plasma CRP is a marker of inflammation associated with a wide variety of disorders ranging from infection to malignancy [25,26]. In recent years, the CRP level in patients with influenza has been of interest to researchers. Morton et al. (2017) suggested that CRP is a crucial parameter for determining the admission, observation, or discharge of H1N1 influenza patients [27]. Based on their work, the CRP determinant was the most important predictor of safe discharge. In another survey, Li and co-workers found that CRP levels could indicate which febrile children under three months of age should undertake blood culture tests during influenza seasons [28]. In the present study, we reported a significant difference between the levels of CRP in the three groups of influenza patients ($P<0.05$). Our results are consistent with those of Kaji et al., who reported a meaningful difference in CRP levels between A-H3N2, A-H1N1, and B influenza subjects in Japan.

For a probable diagnosis of influenza, many non-specific serological parameters have been suggested, such as lymphopenia, monocytosis, thrombocytopenia, and leukocytosis or leukopenia. The WBC count is one of the parameters that has frequently been investigated. In a survey of hospitalized subjects with A-H1N1 influenza during the first two months of its pandemic, leukopenia was observed in 20% of patients. Wiwanitkit et al. (2013) presented leukopenia and lymphopenia as important findings of influenza that can be verified through

blood tests[29]. Soleimani and co-workers reported that the presentation of influenza in children is variable and A-H1N1 influenza may cause leucopenia and thrombocytopenia [30]. As previously mentioned, Kaji et al (2003) reported that influenza A-H3N2 was more severe than A-H1N1 or B in terms of leukopenia[24]. In contrast, we did not find any meaningful difference between the numbers of WBC in the three groups under study.

This retrospective study was confronted with some limitations. Firstly, despite the use of the RT-PCR molecular technique for the definitive diagnosis of the influenza subtype, some of the features seen on CT scans could have been consequences of infections other than influenza. A second limitation was the lack of access to pathological samples of the patients' lungs. As we know, the correlation between radiological and histopathological findings is a considerable issue in influenza. Finally, our study featured a relatively low number of patients, limiting its power.

Conclusions

In summary, the present study compared the clinical, serological, and radiological parameters of patients with three sub-types of influenza to fulfill the present gap in the literature. Fever was the most common clinical manifestation across all three groups. Notably, A-H3N2 subjects had significantly higher fever temperatures and CRP levels as well as meaningfully greater rates of the occurrence of patchy infiltration and middle lobe involvement than A-H1N1 and B-H1N1 subjects. Despite the limitations of the study, its findings are likely to be beneficial in managing patients with influenza and determining the need for further interventions.

Conflict of interest : None declared by all authors.

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Table 1: A summary of clinical manifestations and associated risk factors in subjects with A-H1N1, B-H1N1, or A-H3N2 influenza. Each variable was investigated as a simple 'yes' or 'no'.

Sign/symptoms or risk factors	**A-H1N1 Frequency (n=27)**	**B-H1N1 Frequency (n=10)**	**A-H3N2 Frequency (n=4)**
Fever	25/27 (92.5%)	10/10 (100%)	4/4 (100%)
Headache	20/27 (74.07%)	6/10 (60%)	3/4 (75%)
Gastrointestinal involvement	15/27 (55.5%)	4/10 (40%)	2/4 (50%)
Myalgia	20/27 (74.07%)	7/10 (70%)	4/4 (75%)
Vocal hoarseness	16/27 (59.2%)	4/10 (40%)	1/4 (25%)
Calf pain	12/27 (44.4%)	3/10(30%)	1/4 (25%)
Tachycardia	13/27 (48.1%)	3/10 (30%)	2/4 (50%)
Respiratory involvement	21/27 (77.7%)	6/10 (60%)	3/4 (75%)
Vaccination	11/27 (40.7%)	2/10 (20%)	1/4 (25%)
Contact with birds	2/27(7.4%)	0/10 (0%)	0/4 (0%)
Recent travel	4/27 (14.8%)	0/10 (0%)	0/4 (0%)
Contact with influenza patients	3/27 (11.1%)	1/10 (10%)	0/4 (0%)

Table 2: A summary of serological findings in hospitalized subjects with A-H1N1, N-H1N1, or A-H3N2 influenza. Each variable was assessed as a numerical value.

Serologic variable	**A-H1N1 Mean ± SD**	**B-H1N1 Mean ± SD**	**A-H3N2 Mean ± SD**
ΩB˜ (/μΛ)	7314.4 ± 2437.9	6214 ± 1804.1	6825 ± 2604.3
Lymphocytes (%)	19.9 ± 8.9	21.510 ± 6.9	22.9 ± 5
Neutrophils **(%)**	71.6 ± 9.4	67.6 ± 9.4	79.2 ± 7.3
Πλατελετς (/μΛ)	159333.3 ± 65099.9	192000 ± 83802.6	153250 ± 33826.7
CRP* (mg/L)	2.4 ± 0.4	2.3 ± 0.4	2.9 ± 0.3
ALT (U/L)	30.9 ± 16.0	26.7 ±11.7	30.0 ±11.2
AST (U/L)	34.89 ±11.27	31 ± 11.7	31.25 ± 7.5
LDH (U/L)	275.6 ± 135.3	236.5 ± 86	259 ± 49.846
BUN (mg/dL)	18.63 ± 15.7	11.20 ± 2.9	23.5 ± 21.3
Creatinine (mg/dL)	1.115 ± 0.21	1.0 ± 0.17	1.05 ± 0.17
Hb (g/dL)	13.4 ± 1.6	12.4 ± 1.2	12.8 ± 2.4
ESR (mm/hr)	32.4 ± 24.8	31.9 ± 26.5	45.25 ± 28.8
CPK (U/L)	92.7 ± 35.2	110.4 ± 44.1	125.2 ± 40.9
Bil-T (mg/dL)	0.73 ± 0.5	0.53 ± 0.1	0.6 ± 0.1
Bil-D (mg/dL)	0.3 ± 0.1	0.2 ± 0.1	0.2 ± 0.09

White blood cell (WBC); C-reactive protein (CRP); alanine transaminase (ALT); aspartate transaminase (AST); lactate dehydrogenase (LDH); alkaline phosphatase (ALP); blood urea nitrogen (BUN); hemoglobin (Hb); erythrocyte sedimentation rate (ESR); creatinine phosphokinase (CPK); total bilirubin (Bil-T); and direct bilirubin (Bil-D).

***P<0.05**

Table 3: Summary of the chest CT findings of patients hospitalized due to influenza A-H1N1, B-H1N1, or A-H3N2 disease.

Parameter	**Influenza (No. of patients)**	**Influenza (No. of patients)**	**Influenza (No. of patients)**	**Influenza (No. of patients)**
	H1N1-A (n=25)	**H1N1-B (n=10)**	**A-H3N2 (n=4)**	**P-value**
Normal	5	0	0	.228
Patchy infiltration	8	2	4	.012*
Interstitial infiltration	5	5	0	.069
Pleural effusion	1	0	0	.767
Pleural effusion with infiltration	3	0	0	.432
Unilateral involvement	2	3	1	.186
Bilateral involvement	10	4	3	.353
Upper lobe involvement	0	1	0	.204
Middle lobe involvement	1	2	2	.021*
Lower lobe involvement	6	4	0	.262

***P<0.05**

Figure legends:

Figure 1: Examples of CT scans of the influenza patients; patchy infiltration and middle lobe involvement were two parameters that were present at significantly different rates in the disease caused by three types of influenza subtypes. A: anterior; P: posterior.

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