Is H3N2 Pneumonia Different from Other Community-Acquired Pneumonia?

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Abstract

Objective: To evaluate the clinical, laboratory, radiological, and demographic data of H3N2 pneumonia cases hospitalized to the Pulmonology Department during H3N2 pandemics and compare them with non-H3N2 community-acquired pneumonia (CAP) cases.

Methods: The study population consisted of all CAP cases hospitalized to our Pulmonology Department between December 2013 and February 2014 during the influenza outbreak. The patient files were evaluated for physical findings, laboratory data, radiological findings, and treatment and outcome of cases. H3N2 was diagnosed using polymerase chain reaction (PCR) analysis of throat swabs. The clinical, radiological, and laboratory findings of H3N2 pneumonia cases were compared with those of non-H3N2 pneumonia cases. Mann–Whitney U test, Chi-square test, Fisher's exact test, and logistic regression analysis by the forward step wise method were used for statistical analyses. P value<0.05 was considered significant.

Results: During the H3N2 pandemic outbreak, 69 cases were diagnosed with CAP; 62 (89.8%) with non-H3N2 CAP, and 7 (10.2%) with H3N2 pneumonia. The demographic data, CURB-65, pneumonia severity index (PSI) scores, and clinical, radiological, and laboratory findings of the two groups were similar (p>0.05). The rates of treatment failure and/or transport to the intensive care unit with the need of invasive mechanical ventilation and mortality rates were also similar in both groups (p>0.05).

Conclusion: H3N2 pneumonia/viral pneumonia is a member of CAP. Although the number of H3N2 cases are extremely small to draw a conclusion, the results of this study highlight that the clinical, radiological, and laboratory findings of H3N2 pneumonia cases are not different from those of non-H3N2 CAP cases.

Keywords: H3N2, influenza pandemic, pneumonia

INTRODUCTION

Pneumonia is an inflammation arising from microorganismsin the lung parenchyma. It mainly occurs due to the microaspiration of microorganisms of the oropharyngeal flora. Inflammations due to viral factors, not existing in the oropharyngeal flora of a normal healthy person, start after reaching the lung parenchyma by way of inhalation or droplets are called viral pneumonia. Influenza A, respiratory syncytial virus, adenovirus, parainfluenza types 1, 2, 3, and influenza B are the most common viral agents that cause viral pneumonia (1).

Influenza virus, which is an enveloped single-stranded RNA virus from the Orthomyxoviridae family, is divided into three types-A, B, and C-according to nucleocapsid and matrix proteins. Type A influenza viruses are important pathogens for birds, pigs, horses, and especially for humans. They cause the death of over half a million people in the world every year. In the United States (US), 5–20% of the population is infected with type A influenza virus each year, and about 36,000 people die from diseases associated with influenza A (2-5).

In our country, the first flu in the 2013–2014 flu season was detected in the 43rd week (October 22, 2013) according to the weekly influenza surveillance reports of the Ministry of Health. The percentage of influenza-positive samples in the samples studied increased in comparison to the previous week,

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and as of the 48th week, it was reported that H3N2 (influenza type A) was seen more in this season than were the other types of influenza (6).

Our study was planned retrospectively in order to evaluate the results of treatment and demographic, clinical, laboratory, and radiological features of the patients hospitalized at Chest Diseases Clinic with a diagnosis of H3N2 pneumonia in the 2013–2014 flu season and during H3N2 pandemic and to compare with the features of other pneumonia patients-i.e., other than those infected with H3N2-who were hospitalized with the diagnosis of community-acquired pneumonia (CAP) in the same period.

METHODS

In the December 2013–February 2014 flu season, a total of 83 patients who were hospitalized in the Chest Diseases Clinic of Dr. Lütfi Kırdar Kartal Training and Research Hospital with the diagnosis of pneumonia were analyzed retrospectively. Because of having hospital-acquired pneumonia and, 14 of these patients were excluded from the study. In accordance with the Diagnosis and Treatment Reconciliation Report (RR) for CAP in adults of the Turkish Thoracic Society (TTS), 69 patients diagnosed with pneumonia were included in the study (7). Demographic data; anamnesis, physical examination findings (PE); and clinical, radiological, and laboratory characteristics of the patients included in the study were recorded. Moreover, treatments administered to all patients and invasive mechanical ventilation (IMV) or noninvasive mechanical ventilation (NIMV) and intensive care support use/requirements were recorded during the treatment process. For the diagnosis of H3N2, nasopharyngeal/throat swab samples were taken from all patients admitted with the diagnosis of CAP between the work dates. For this, on the first day of the hospitalization, patient's nasopharyngeal or nasal swab samples were taken with a special swab by the doctor or assistant health personnel who were trained on this issue previously and transported to a virology laboratory determined by the Ministry of Health in a viral transport medium in accordance with the cold chain and biosafety rules. The results were reported from the center within a maximum of 48 hours. While the results of swab samples of the cases sent with the suspicion of pandemic H3N2 were awaited, oseltamivir (150–300 mg/day) oral therapy was started empirically to patients with high clinical suspicion. Simultaneously with this treatment, an appropriate antibiotic was also started in accordance with the TTS-CAP-RR (7). Patients whose H3N2 diagnosis was found positive in the swab sample and who were treated with the diagnosis of pneumonia and the patients whose H3N2 diagnosis was found negative and got the diagnosis of other CAP were divided into two groups and their data were documented. The diagnosis of H3N2 pneumonia was made in the presence of lesions whose H3N2 virus was proven in swab sample, that are consistent with the clinic of pneumonia and suggest pneumonia radiologically.

In both groups, demographic data such as age, gender, comorbidities, symptoms, PE findings, posterior-anterior chest radiograph (PACR) and computed tomography (CT) findings, laboratory findings, arterial blood gas (ABG) results, hospitalization time, CURB-65 in accordance with TTS-CAP-RR, pneumonia severity index (PSI) scores, and MV (IMV and/or NIMV) support/intensive care necessity were recorded and compared with each other.

Statistical Analysis

Statistical analysis was performed using the software SPSS 17.0 (Statistical Package for the Social Sciences Statistics for Windows, Version 17.0.; Chicago, IL, USA). Continuous variables were expressed as mean±standard deviation and categorical variables as percentage in descriptive statistics. Because the number of samples in the H3N2 group is low, non-parametric tests were used in the intergroup comparisons. While the Mann–Whitney U test was performed for the comparisons of continuous variables, chi-square or Fisher's exact test was used for categorical data. In all study groups, the effect of H3N2 pneumonia on the requirement of MV support/intensive care for the treatment during the hospitalization was assessed with exact logistic regression analysis method. $p<0.05$ was accepted significant for statistical significance in all tests.

RESULTS

A total of 69 CAP patients, 7 (10.2%) of whom had H3N2 pneumonia, were included in the study. In the H3N2 pneumonia group, 6 (85.7%) patients were female and 1 (14.3%) was male; their mean age was 57.4±21.5 years (min: 25 max: 95). The most common symptoms were cough (100%), and the most common PACR finding was reticular appearance in all bilateral zones and the most common concomitant disease was chronic cardiovascular system diseases (71.4%). Clinical, radiological, demographic findings, CURB-65 values, and PSI scores of the cases in the H3N2 pneumonia group are summarized in Table 1, laboratory values in Table 2 and the antibiotic treatment that was started empirically in Table 3. In this group, blood and sputum cultures of all of the cases were sent and no reproduction occurred in cultures. MV support was applied in 5 of the patients (71.4%) (NIMV in 3 cases and IMV in 2 cases) in intensive care, 7 (100%) patients were discharged with recovery and none of the patients died. The total number of the days of staying at the hospital is 8.29±7 days in this group.

In the CAP group, 29 (46.8%) patients were female and 33 (53.2%) of patients were male; the mean age was 67.2±16.1 years (min: 22 max: 90). The most common symptom was cough (88.7%), the most common PACR finding was unilateral infiltration (56.5%) and the most common comorbidity was chronic cardiovascular system diseases (45.1%). Clinical, radiological, and demographic findings; CURB-65 values; and PSI scores of the patients in this group are summarized in Table 1, laboratory values in Table 2, and antibiotic treatment that was started empirically in Table 3. Sputum culture was taken in 28 (45.2%) of the cases, reproduction occurred in 2 of them (3.2%) and the most frequently reproducing microorganism was *Pseudomonas aeruginosa* in two cases. Blood cultures from 35 patients (3.2%) were sent; reproduction occurred in 4 of these cases, and *Staphylococcus hominis* was the reproducing microorganism in these 4 cases. MV support was applied in 17 cases (27.4%) in intensive care (NIMV in 7 cases and IMV in 10 cases), 1 (1.6%) patient died, and 68 (98.4%) patients were discharged with recovery. The total stay at the hospital in this group was 7.11±4.9 days.

Mortality rates, CURB-65, PSI scores, and most demographic, clinical, and laboratory values were not significantly different between the two groups evaluated in our study. Although a tendency was seen in favor of H3N2 pneumonia in female gender (85.7% vs. 46.8%, $p=0.11$), the difference between the two groups was not statistically significant. Although there is a tendency in favor of the H3N2 group in terms of body temperature (37.46±1.00 vs. 37.02±0.48) and in favor of other pneumonia in terms of white blood cell count (13377±6353 vs. 10377±3147), the differences are not statistically significant ($p>0.05$). The symptom of nausea was found significantly more frequently in the H3N2 group (28.6% vs. 1.6%, $p=0.026$). Bilateral crackles and rhonchus auscultation were observed more in the H3N2 group, but the difference was not found significant (57.1% vs.

Table 1. Clinical, radiological, and demographic findings of the patients

	H3N2 pneumonia (n=7)	Other CAP (n=62)	p
Age (mean±SD)	57.4±21.5	67.2±16.1	0.170
Gender			
Number (F/M)	6/1	29/33	0.052
Percent (F/M)	85.7%/14.3%	46.8%/53.2%	
Smoking (pack-years)	12.8	18.5	0.247
Comorbidities			
No/Yes	0/7	12/50	0.204
Chronic CVS disease	5 (71.4%)	28 (45.1%)	0.301
Chronic lung disease	(42.8%) 19	(30.6%)	0.292
Chronic kidney disease	1 (14.2%)	5 (8%)	0.963
Cerebrovascular disease	0	7 (11.2%)	0.702
Other	1 (14.2%)	11 (17.7%)	0.297
Symptom			
Cough	7 (100%)	55 (88.7%)	0.352
Sputum	7 (100%)	50 (80.6%)	0.204
Shortness of breath	7 (100%)	48 (77.4%)	0.162
High fever	5 (71.4%)	30 (48.4%)	0.105
Nausea and vomiting	2 (28.6%)	1 (1.6%)	0.056
Other	3 (42.9%)	15 (24.2%)	0.452
Physical examination			
Normal	1 (14.3%)	3 (4.8%)	0.603
Bilateral crackles and rhonchus	4 (57.1%)	14 (22.8%)	0.057
Bilateral crackles	2 (28.6%)	17 (27.4%)	0.333
Unilateral crackles	0	15 (24.2%)	0.949
Rhonchus	0	11 (17.7%)	0.340
Decreased breath sounds	0	2 (3.2%)	0.987
NBM (/min)	23.71±3.7	23.1±5.2	0.801
CAB (mmHg)	106±18.7	93.8±17.7	0.055
SBP (mmHg)	127.2±18.7	122.4±24.4	0.460
DBP (mmHg)	72.5±7.1	69.3±13.1	0.289
Fever (°C)	37,4±0,4	37±1	0.088
PACR			
Reticular appearance in all bilateral zones	3 (42.9%)	7 (11,3%)	0,057
Bilateral focal infiltrates	3 (42.9%)	12 (19.4%)	0,169
Bilateral infiltration	1 (14.3%)	35 (56.5%)	0,049
Pleural fluid and consolidation	0	3 (4.8%)	1
Thoracic CT not taken	1 (14.3%)	28 (45.2%)	0.225
Reticular appearance in all bilateral zones	2 (28.6%)	3 (4.8%)	0.596
Bilateral focal infiltrates	2 (28.6%)	10 (16.1%)	0.777
Unilateral infiltration	1 (14.8%)	15 (24.2%)	1
Pleural fluid and consolidation	1 (14.3%)	6 (9.7%)	0.487
CURB-65	0.86±0.37	1.63±1.1	0.087
PSI score	3.1±0.89	3.5±1.1	0.41
PSI point	90.7±28.2	98.7±34.5	0.55

CAB: Cardiac apex beat; CAP: community-acquired pneumonia; CT: computed tomography; CVS: cardiovascular system; DBP: diastolic blood pressure; F: female; M: male; NRM: number of breaths/min; PACR: posterior anterior chest radiograph; PSI: pneumonia severity index; SBP: systolic blood pressure; SD: standard deviation

21.0%, p=0.057). Although reticular pattern was observed more in both PACR and CT in the H3N2 group (PACR 42.9% vs. 11.3%, p=0.057; CT 28.6% vs. 4.8%, p=0.077), the difference was not significant.

Although the frequency of NIMV addition to the treatment showed a tendency in favor of H3N2 pneumonia, the difference was not statistically significant (42.9% vs. 11.3%, p=0.057). In the exact logistic regression analysis carried out to determine the independent variables that were effective on the addition of NIMV or IMV to the treatment in the intensive care unit (ICU), it was seen that H3N2 pneumonia did not have an effect on the endpoint in the univariate analysis (OR=6.41, exact p=0.059), and none of them was effective independently on the endpoint in multivariate analysis (all exact p>0.05).

DISCUSSION

The aim of our study was to evaluate the demographic, clinical, laboratory, and radiological features and treatment results of the H3N2 pneumonia patients who bring an unexpected load to the health system, especially during epidemics, and who have a high morbidity and mortality in the patient group of high risk and to share with the literature by comparing them with the characteristics of other patients hospitalized with the diagnosis of community-acquired pneumonia (CAP) in the same period. In the influenza epidemic period of 2013–2014, a total of 69 patients were hospitalized due to CAP and 7 of them (10.1%) were diagnosed with H3N2 pneumonia. When the clinical, radiological, and laboratory values were compared between H3N2 pneumonia and the other CAP group, no statistically significant differences were found in our study.

Seasonal flu outbreaks are among the major worldwide causes of morbidity and mortality. Studies have shown that 5–20% of the US population is infected with influenza every year and that 3000–49000 people die due to diseases associated with influenza every year (8). In our country, H3N2 cases that were sporadically seen first in the 43rd week of 2013 started an epidemic, in which it was dominant, as of the 48th week. A total of 1662 samples were sent to Turkey Influenza

Table 2. Laboratory findings of the patients

	H3N2 pneumonia (n=7)	Other CAP (n=62)	p
Hemoglobin (g/dL)	11.6±2.1	13.8±12	0.438
Hematocrit (%)	34.9±6.2	36.9±6.1	0.544
White blood cell (/µl)	10377±3146	14334±6358	0.071
Platelets (/µL)	237000±55818	252168±140289	0.655
Sedimentation (mm/h)	58±36.6	59.2±25.4	0.889
Serum-reactive protein (mg/L)	139±130.5	155.4±120.2	0.711
INR	1.4±0.98	1.3±0.5	0.314
Urea (mg/dL)	49±33.3	65.8±44	0.315
Creatinine (mg/dL)	1.6±2.3	1.2±0.9	0.538
Sodium (mEq/L)	133±3.6	135±4.3	0.364
Potassium (mEq/L)	4.3±1.2	4.3±0.6	0.605
Calcium (mEq/L)	8.7±0.7	8.5±0.7	0.992
Chloride (mEq/L)	96.1±5	100±4.7	0.116
Total protein (g/dL)	6.5±0.7	6.6±0.8	0.681
Albumin (g/dL)	3.4±0.6	3.4±0.6	0.894
Alanine transaminase (U/L)	17.8±12.6	24.5±22	0.320
Aspartate transaminase (U/L)	47.4±70	32.7±28.3	0.788
Procalcitonin (mg/L)	0.066±0.0056	4.89±10.2	0.195
Arterial blood gas values			
pH	7.37±0.09	7.43±0.06	0.160
PaO_2 (mmHg)	45±9.7	52.8±10.1	0.133
$PaCO_2$ (mmHg)	45.5±16.2	38.4±10.7	0.247
HCO_3 (mEq/L)	26.1±9.7	25.4±6.4	0.878
Oxygen saturation (%)	78.9±12.9	85.7±11	0.119

CAP: Community-acquired pneumonia; INR: international normalized ratio

Table 3. Initiated empirical antibiotics of the cases

	H3N2 pneumonia (n=7)	CAP (n=62)
Injectable third generation cephalosporin	3 (42.9%)	8 (12.9%)
Injectable third generation cephalosporin + oralmacrolide	2 (28.6%)	37 (59.7%)
Moxifloxacin	1 (14.3%)	12 (19.4%)
Oral second-generation cephalosporins	1 (14.3%)	2 (3.2%)
Other	0	3 (4.8%)

CAP: Community-acquired pneumonia

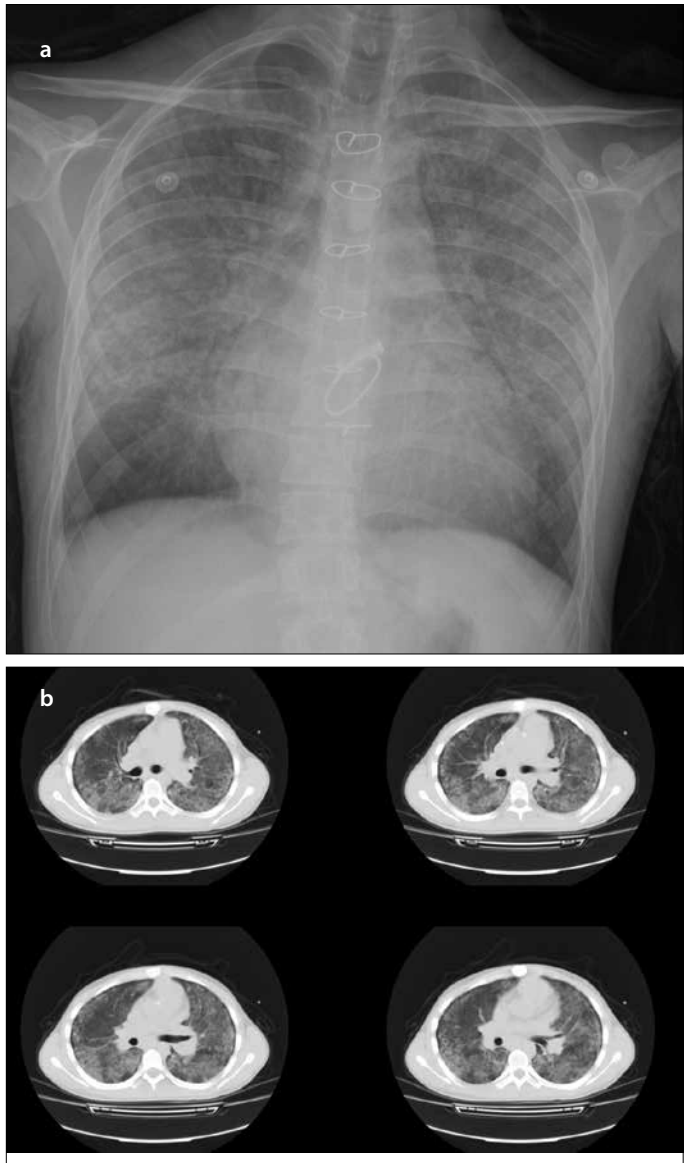

Figure 1. a, b. The reticular appearance in all bilateral zones chest radiograph of cases diagnosed with H3N2 pneumonia (a). Bilateral diffuse interstitial pattern in parenchymal sections in computed tomography of the patients with H3N2 pneumonia (b)

Laboratory of Public Health Center and the National Influenza Reference Laboratory of İstanbul School of Medicine and 195 of them were identified as influenza. Of these, 172 (88%) were classified as H3N2 (9).

We determined the prevalence of H3N2 pneumonia as 10.1% in all pneumonia patients treated in our clinic. Apisarnthanarak et al. (10) examineda total of 145 cases in the study to compare the risk factors of patients with H3N2 and H5N1 pneumonia and reported that the mean age of the patients with H3N2 pneumonia was 72; the proportion of males was 50%; the proportion of females was 50%; the first distinct symptoms of the majority of the cases (90%) were lung symptoms such as cough, phlegm, and shortness of breath; and the concomitant diseases were lung diseases (50%), diabetes mellitus (30%), cardiovascular diseases (20%), and cerebrovascular diseases (10%), and they also reported a close-ratio (7%) to our study in terms of the incidence of H3N2 pneumonia in their study. In our study, the

average age of patients with H3N2 pneumonia was 57.4; the proportion of males was 14.3%; the proportion of female patients was 85.7%; the most common symptoms were cough (88.7%), sputum (80.6%), and dyspnea (77.4%); and the most common comorbidities were chronic cardiovascular system diseases (71.4%), chronic lung diseases (42.8%), and chronic kidney diseases (14.2%).

Pulmonary complications of viral pneumonia can be grouped under four main headings. These are primary viral pneumonia, bacterial pneumonia developing secondary to viral infection, viral pneumonia developing in immunosuppressed patients, and acute exacerbation of chronic obstructive pulmonary disease due to viral agents. The predominant radiological finding in primary viral pneumonia is in the form of bilateral interstitial or patchy infiltration areas (11). In our study, 7 of a total of 69 pneumonia cases were diagnosed with primary H3N2 pneumonia. When the chest radiographies of our cases were examined, it was observed that predominant radiological pattern was bilateral interstitial involvement consistent with the literature (Figure 1). In PACR, the rate of bilateral reticular appearance was 46.9%, and in thoracic CT, this rate was 28.6%. There are not many studies on radiological findings of H3N2 pneumonia in the literature. In a study they conducted with H1N1 pneumonia patients, Agarwal et al. (12) found bilateral involvement on chest radiograph of all 14 patients who had severe respiratory failure and needed MV at the time of admission. Similar to this result, involvement was bilateral on chest radiographs of 3 H3N2 pneumonia patients who needed the support of NIMV in our study as well.

Although the frequency of NIMV addition to the treatment showed a tendency in favor of the H3N2 pneumonia group, the difference between was not statistically significant in the exact logistic regression analysis. In the study where they compared the patients with H1N1 and H3N2 pneumonia, Yang et al. (13) could not identify clinically significant difference between the groups, but they found a more severe inflammatory response in H3N2 pneumonia with the measurement results of interleukin and chemokine. In the article where they reported 2 patients who they followed in ICU due to H3N2 pneumonia diagnosis and the development of acute respiratory distress syndrome (ARDS), Peris et al. (14) expressed that flu-like symptoms in patients with H3N2 could not always progress in a mild and self-limiting picture and that the patient could be followed in ICU due to serious complications at older ages and according to underlying medical conditions and these patients could even be lost. In this case report, they lost one of two patients with H3N2 pneumonia and ARDS; they also reported that H3N2 virus could lead to diffuse alveolar damage; necrosis in bronchi, bronchioles, and epithelium; and severe inflammation in airways. We have not found a study comparing the mortality between H3N2 pneumonia and other CAP in the literature; when the studies in the form of case reports were examined, we saw that H3N2 pneumonia cases could remain quite mortal. In March 2012, it was reported to United States Disease Prevention and Control Center that 3 H3N2 pneumonia cases in the same family applied to the medical institution with the complaints of fever, shortness of breath and bloody sputum, patients were infected with the H3N2 virus and died after the development of co-infection with staphylococcus aureus, and it was also remarked that H3N2 virus infection could have a high mortality (15).

The most important limitation of our study is that it is not statistically strong enough because of the small number of cases, especially in the H3N2 pneumonia group. This is because the study was planned to be single centered and retrospective.

CONCLUSION

In this study, the number of cases in this group remained limited because the cases diagnosed with pneumonia only radiologically/clinically and the patients with a certain diagnosis of H3N2 pneumonia as a result of the nasopharyngeal/throat swab were included in H3N2 pneumonia group. Though we could not reach certain judgments with a limited number of patients, in the study where we compared CAP and H3N2 pneumonia, we did not detect a statistically significant difference between the radiological and laboratory values in two groups. In this regard, there is a need for multicenter studies with more patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of local ethic committee.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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