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Original Article

Viral etiology in adult influenza-like illness/acute respiratory infection and predictivity of C-reactive protein

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Abstract

Introduction: Influenza-like illness (ILI) and acute respiratory infection (ARI) are common presentations during winter and indiscriminate antibiotic use contributes significantly to the emerging post-antibiotic era.

Methodology: Otherwise healthy 152 patients, presenting to outpatient clinics with ILI/ARI, were included. Patients had history & physical, CRP, hemogram and nasopharyngeal swabs for rhinovirus A/B, influenza A/B, adenovirus A/B/C/D/E, coronavirus 229E/NL63 and OC43, parainfluenza virus 1/2/3, respiratory syncytial virusA/B, metapneumovirus and *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella pneumophila* and *Bordetella pertussis* by PCR and for ABHS culture.

Results: Median (IR) age was 26.5 (16.5). Time to presentation was shorter in men ($p = 0.027$). Patients with rhinovirus had lower rates (20%) of myalgia ($p = 0.043$). Patients with influenza virus had higher rates (97%) of elevated CRP ($p = 0.016$). Logistic regression revealed that patients with ILI/ARI and CRP $\geq$ 5 mg/L were 60 times more likely to have influenza virus infection than other viral agents (OR = 60.0, 95% CI = 2.65 to 1,358.2, $p = 0.010$). Rhinovirus predominated in December (54%), March (36%), and April (33%). Influenza virus predominated in January (51%). Fever was most common with adenovirus ($p = 0.198$). All GABHS cultures were negative. Atypical organisms and *Bordetella pertussis* were negative in all but one patient.

Conclusions: Influenza virus is the most likely pathogen in ILI/ARI when CRP $\geq$ 5 mg/L. This might be explained by tissue destruction. Myalgia is rare with rhinovirus probably due to absence of viremia. Negative bacteria by PCR and culture suggest unnecessary antibiotic use in ILI/ARI.

Key words: acute respiratory infection; influenza-like illness; viral agents.

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Introduction

Influenza-like illness (ILI) and acute respiratory infection (ARI) have been monitored by the Influenza Incidence Surveillance Project (IISP). Although bacterial etiology might sometimes be encountered, the majority of ILI cases are caused by viral pathogens [1]. Epidemic peaks during the winter months are usually caused by influenza virus and respiratory syncytial virus (RSV), while other viruses such as human metapneumovirus (MPV) and parainfluenza viruses (PIVs) also circulate in fall and winter [2]. There is a corresponding winter increase in presentations to emergency departments and outpatient clinics [3,4].

Although viral agents causing ARI/ILI predominate in winter, they are usually indistinguishable from bacterial agents or each other on clinical grounds alone [5]. Rapid antigen tests and molecular diagnosis can help distinguish bacterial from viral etiology, but while not all bacterial species have approved tests, positive results do not always indicate disease causation. The issue becomes more complicated in clinical practice of ARI/ILI treatment. In general, there is a widespread tendency to prescribe antibiotics for ARI/ILI in Turkey and other countries [6].

C-reactive protein (CRP) is an acute-phase reactant that is elevated in response to inflammatory stimuli. It is synthesized in the liver and regulated by tumor necrosis factor (TNF) and interleukin-6 (IL-6). Its value in discrimination of bacterial from viral infections has been studied with various results, but predictivity of CRP among viral agents has not been studied. On the other hand, differentiating influenza virus from other

respiratory viruses is of prime importance because the influenza virus is associated with higher morbidity and mortality, is potentially preventable by vaccination, and can be managed with specific antivirals [7,8].

Models for prediction of influenza infections by clinical signs and symptoms were developed during epidemics [9,10]. Case definitions yielded variable performance for influenza surveillance, which would be probably best optimized according to the objectives of the program [8, 11-13]. We designed this study to evaluate the viral and bacterial etiology as well as clinical and laboratory characteristics of adult outpatients presenting with ARI/ILI in the winter season of 2013–2014

Methodology

A total of 152 patients presenting to the emergency department, internal medicine, and infectious disease outpatient clinics with ILI/ARI symptoms from 1 Dec 2013 to 6 April 2014 were included. This study was approved by the ethics committee for clinical research of the Sakarya University School of Medicine with the number 16214662.050.01.04/53 on 11 Dec 2013. ILI case definition included sudden onset of symptoms plus at least one of the following four systemic symptoms: fever or feverishness, malaise, headache, myalgia; plus at least one of three respiratory symptoms (cough, sore throat, and shortness of breath). ARI was defined according to following criteria: sudden onset of symptoms plus at least one respiratory symptom (cough, sore throat, shortness of breath, coryza) and a clinician's judgment that the illness was due to an infection [14].

Inclusion criteria were age 18–55 years, having ILI/ARI per the definitions, and informed consent for inclusion in the study. Exclusion criteria were having co-morbid disease (including diabetes mellitus, chronic liver, lung, or kidney disease), malignancy, being immunosuppressed or compromised, thyroid dysfunction, being admitted to hospital in the previous 30 days, having received antibiotics in the last 7 days, and pregnancy. All patients had history taken and a physical exam done. Vitals and SpO2 were recorded. Complete blood count (CBC) with differential, serum CRP, and a chest X-ray were obtained from each patient. Two nasopharyngeal swabs were taken from all patients. One set of samples were sent for culture group A β-hemolytic streptococci (GABHS). They were applied to a blood agar plate and incubated at 37C° for 18–24 hours. Other samples were stored at -80°C and were studied by multiplex polymerase chain reaction (PCR) for detection of rhinovirus A/B, influenza A/B, adenovirus A/B/C/D/E, coronavirus 229E/NL63 and OC43, parainfluenza virus 1/2/3, respiratory syncytial virus A/B, and MPV as well as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella pneumophila*, and *Bordetella pertussis* upon completion of sample collection.

Nucleic acid extraction and detection assays

Nucleic acids were extracted from up to 300 µL of each specimen by GeneAll Ribospin vRD II (GeneAll Biotechnology Co. Ltd., Seoul, South Korea) viral DNA/RNA isolation kit. The final elution volume of each sample was 30–50 µL.

RV12 testing was performed using a Seeplex RV12 ACE detection kit (Seegene Inc., Seoul, Korea). Random hexamer-primed complementary DNA (cDNA) synthesis products were generated using the Revertaid First Strand cDNA synthesis kit (Fermentas Inc., Burlington, Canada), according to the manufacturer's instructions. Each cDNA preparation was subjected to the RV12 PCR procedure according to the manufacturer's instructions (Seegene Inc., Seoul, Korea).

Briefly, parallel 20 µL reactions were set up, each containing RV12 mastermix, 8-MOPS contamination control reagent, 5X RV12 ACE primer (A or B) (Seegene Inc., Seoul, Korea), and 3 µL cDNA. One of each pair was supplemented with 4 uL primer mix A, and the other with 4 uL primer mix B. Thermal cycling conditions were as follows: 15 minutes at 94°C, followed by 40 cycles of 94°C for 30 seconds, 60°C for 90 seconds, and 72°C for 90 seconds, followed by a single incubation of 10 minutes at 72°C. Amplification products were detected using capillary electrophoresis technology (Lab901 Screentape System; Agilent Technologies Inc., Santa Clara, CA, USA). For bacteria other than streptococci, a Seeplex Pneumobacter ACE Detection kit (Seegene Inc., Seoul, Korea) was used. The assay was performed according to the manufacturer's instructions. DNA extraction and assay procedure were previously explained in detail by Cho *et al*. [15]. Standard agar cultures were used for GABHS detection.

Statistics

Normally distributed data were reported as mean and standard deviation (SD), whereas non-normally distributed data were reported as median and interquartile range (IR). Normally distributed data were compared among groups by one-way analysis of variance (ANOVA) test, and the Mann-Whitney U test was used for non-normally distributed data. Categorical

associations were evaluated using Chi-square statistics and multiple logistic regression. SPSS 10.0 (SPSS Inc., Chicago, USA) was used for statistical analysis. All p values less than 0.05 were considered significant.

Results

There were 70 male (46.1%) and 82 female (53.9%) patients. Other demographic and laboratory characteristics are presented in Table 1. Time to presentation was significantly shorter in male compared to female patients (55.9 hours vs. 70 hours, respectively; p = 0.027). The most frequent symptom was sore throat, whereas the most frequent sign was pharyngeal hyperemia (Table 2). ILI and ARI was diagnosed in 65 and 87 patients, respectively. At least one viral agent was detected in 105 patients (69.1%). Rhinovirus and influenza virus were co-detected in four patients. MPV was detected in only one patient and it was together with rhinovirus. Distribution of viruses according to months is illustrated in Figure 1. Viral agent detection rates according to type were as follows: rhinovirus A/B 23%, influenza A/B 20.4%, human coronavirus 8.6%, human paraifluenza 2/3 7.9%, human adenovirus 5.9%, and MPV < 1%. Influenza A (n = 31) was the second-most detected virus. Influenza B was detected in three patients. Characteristics of influenza A/B detected patients are shown in Table 2. The mean (SD) age was 34 (13). The most frequent symptom was coryza (87.1%), followed by malaise (74.2%). Fever was present in 26 of 31 patients with influenza virus (83.9%). ARI definition had a sensitivity of 100% and a specificity of 0.82%. In diagnosing ILI, when cough or sore throat alone were used, sensitivity decreased to 96.5% and specificity increased to 9%; when both were used, sensitivity was 100% and specificity decreased to less than 1%.

Table 1. Clinical and laboratory characteristics of patients with/without detected viral etiology (n = 152).

Parameters	Viral etiology detected	No. viral infection	P
n	105	47	
Age, mean (SD) or median (IR)	26 (17)	31 (10)	NS
Duration of symptoms (days), median (IR)	2 (2)	2 (1)	0.027
Temperature (°C), median (IR)	37.3 (0.8)	37.3 (0.77)	NS
Pulse rate, mean (SD)	99.8 (19)	97.5 (15)	NS
Respiratory rate, median (IR)	13 (2)	14 (3)	0.025
Blood pressure (mmHg), mean (SD)	56.7 (11.1)	55.6 (13)	NS
SpO2 (%), median (IR)	98 (2)	98 (1)	NS
CRP (mg/L), median (IR)	9.5 (18.1)	10.7 (14.4)	NS
Hgb (mg/dL), mean (SD)	13.1 (1.8)	13.3 (1.5)	NS
WBC (10^3/µL), median (IR)	9.5 (3.1)	8.4 (2.7)	0.023
Plt (x1,000), mean (SD)	245 (63)	225 (54.7)	NS
Neutrophils (%), mean (SD)	67.3 (10.7)	65 (10)	NS
Lymphocytes (%), mean (SD)	22.6 (9.4)	23.5 (8.8)	NS
Eosinophils (%), median (IR)*	1.6 (1.5)	1.9 (1.4)	NS
Basophils (%), mean (SD)	0.7 (0.4)	0.9 (0.5)	0.044
Monocytes (%), mean (SD)	7.9 (2)	8.9 (3.2)	NS

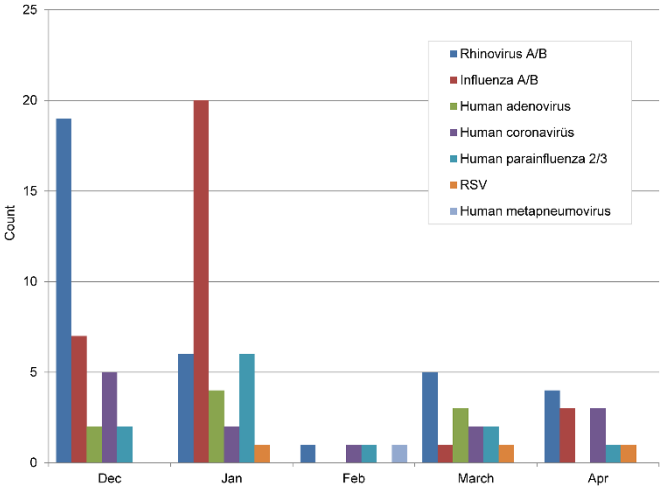
SD: standard deviation; IR: interquartile range; NS: not significant.

Table 2. Symptoms/signs and smoking status according to viral etiology in ILI/ARI patients (n = 105).

Symptom/sign, smoking status, %	Rhinovirus A/B	Influenza A/B	Adenovirus A/B/C/D/E	Coronavirus 229E/NL63 and OC43	Parainfluenza 1/2/3	P
Sore throat	94.3	100	88.9	100	100	NS
Coughing	54.3	64.7	55.5	46.2	58.3	NS
Fever	68.6	85.3	100	69.2	66.7	NS
Headache	34.3	23.5	11.1	30.8	25	NS
Malaise	57.1	70.6	55.6	46.2	58.3	NS
Pharyngeal hyperemia	54.3	67.6	77.8	61.5	75	NS
Coryza	80	82.2	77.8	92.3	91.7	NS
Myalgia	20	35.3	66.7	30.8	58.3	0.034
Smoking	37.1	44.1	50	46.2	33.3	NS

NS: not significant.

Figure 1. Distribution of viral etiology in influenza-like illness/acute respiratory infection during the 2013–2014 flu season.



Current smokers constituted 35.8% of the patients; there was no statistically significant association between viral agents and smoking status (p = 0.865). Patients with rhinovirus had significantly lower rates of myalgia (20%) compared to patients with other viral agents (p = 0.043).

CRP was high (≥ 5 mg/L) in 79 of the viral agent detected patients (67.8%). Patients with influenza virus had significantly higher rates of elevated CRP (97%) compared to other viral agent detected patients (p = 0.016). Logistic regression analysis revealed that patients with ILI/ARI whose CRP was ≥ 5 mg/L were 60 times more likely to have influenza virus infection rather than infection with other viral agents (odds ratio [OR] = 60.0, 95% confidence interval [CI] = 2.65 to 1,358.2, p = 0.010). Rhinovirus was the predominant agent in ILI/ARI during December (54%), March (36%), and April (33%), while influenza virus was the most common agent in January (51%). The weather forecast during the study period also reported the lowest temperature reading (-10°C) and lowest mean temperature (5.9°C) in January.

The median (IR) white blood cells (WBCs) was 8.7 (2.9), and there was no statistically significant difference in WBCs between viral agents (p = 0.137). Fever was most common in patients with adenovirus, but the difference was not statistically significant (p = 0.198).

Mycoplasma pneumonia was detected in one patient, and Seeplex Pneumobacter ACE detection kit (Seegene Inc., Seoul, Korea) results were negative in all of the remaining patients. None of the cultures were positive for GABHS. No viral or bacterial etiology was detected in 47 patients.

Discussion

To the best of our knowledge, this is the first study on the etiology of ILI/ARI in an adult population in Turkey, and we detected at least one viral agent in 69.1% of 152 patients. Our study revealed that ILI/ARI etiology stayed viral all through the 2013–2014 winter and fall season. In order to document etiologic agents in the flu season, we distributed the dates of sampling as much as possible. Despite this effort, we could not detect any bacterial agent in all but one sample during this period. This was in contradiction with some older studies, which reported around 2%–10% atypical bacteria in ILI/ARI patients [16-18]. We also expected to detect more cases with especially atypical bacteria in our study but realized that our results were in agreement with a recent study of outpatients presenting with ILI/ARI where the investigators similarly could not detect any bacterial etiology [19]. We suggest that our results represent the true etiology of ILI/ARI in our region, as otherwise we could detect more than one case, given our sampling distribution over five months.

In our study, the most frequent viral agent detected in ILI/ARI patients was rhinovirus, which was closely followed by influenza virus. This finding partially agreed with those of the study conducted by Zimmerman *et al*. [20], as influenza was followed by coronavirus and RSV in their study. We suggest that this difference was due to the age characteristics of the study populations, which included infants and children ≥ 6 months of age in Zimmerman *et al*.'s study. Similarly, the predominant viruses in the study from Brazil mentioned above [19], influenza and rhinovirus, were not as prevalent as in our study. This difference may be due to the non-temperate climate in our region, as higher activity of influenza virus can be encountered in regions with a humid climate [21]. On the other hand, our rhinovirus detection rates were very close to those of influenza virus, and our results agreed with a large IISP of outpatients from the United States in that the predominant virus was influenza, closely followed by rhinovirus, among adult patients 18–64 years of age [2].

Predictive value of CRP in ILI/ARI etiology has not been studied extensively. One study reported CRP to be predictive for bacterial infection among adults with ILI [22]. Their receiver operating characteristic (ROC) analysis-derived cut-off for CRP was 20 mg/L, and their cases included bacterial pneumonia and other bacterial infections such as streptococcal pharyngitis and peritonsillar abscess. Median (IR) of CRP was 10.4 (15.4) mg/L in our study, and we excluded patients with severe bacterial infections on clinical and laboratory grounds, including cultures for GABHS. On the other

hand, we could not extrapolate about the predictive role of CRP for bacterial infections as we could not detect any bacterial etiology. The predictive role of CRP for influenza among other viruses was reported in a few studies. In a retrospective study, low CRP levels together with some CBC parameters and symptoms were found to be predictive for H1N1 influenza in Europe during the 2009 pandemic [23], whereas another study from China during the same pandemic reported elevated CRP and neutrophils as being the most significant lab findings in initial H1N1 cases [24]. Although we found myalgia to be significantly less common in rhinovirus infection compared to other viruses, WBCs to be significantly lower, and basophil counts to be significantly higher in viral infection detected patients, we could not find any predictive role of symptoms and other laboratory tests for influenza virus. We believe that different results mainly existed because of different geographical regions and different characteristics of H1N1 infection. On the other hand, our findings agreed with those from a German study reporting that clinical symptoms could not predict influenza infection [25]. Interestingly, analogous to our study, abnormal CRP was the most sensitive screening tool for influenza in a recent study from an ambulatory stem-cell transplant center during an influenza outbreak [26]. It is clear that elevated CRP is not expected with viral infections, but our findings revealed that CRP levels can increase in ILI/ARI when the etiology is influenza A/B and this provides a highly predictive tool in making a diagnosis of this agent. This might be due to tissue destruction with influenza infection. Another suggestion from our study was not to accept elevated CRP level alone as bacterial ILI/ARI infection [27].

Finally, fever was the most common sign with influenza virus, and this finding agreed with that reported in a study by Bellei *et al*. [28]. Coryza and malaise were the most frequent symptoms; this was in agreement with the findings of the only viral etiology study of ILI/ARI in our country, which was conducted among children [29]. Although myalgia was present with all viral agents in ILI/ARI, it was least frequent with rhinovirus infection (20%) in our study. This might be explained by the absence of viremia in rhinovirus infection.

Conclusions

We investigated the viral and bacterial etiology of ILI/ARI among adults for the first time in our country during a flu season and documented the distribution characteristics of the etiologic agents. We also reported the related signs/symptoms and laboratory findings. We found that the etiology of ILI/ARI was mainly viral and that elevated CRP had a high predictive value for infection with influenza A/B compared to other viruses studied. Thus, we propose that indiscriminate antibiotic use should be avoided in adult ILI/ARI patients, and once bacterial etiology is excluded, elevated CRP should be taken to suggest influenza virus infection in these patients.

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