■ Original Article

A retrospective study of influenza rapid antigen test positivity with drug prescribing and clinical symptoms

Influenza hızlı antijen test pozitifliğinin ilaç reçetelendirilmesi ve klinik belirtiler açısından değerlendirilmesi üzerine retrospektif çalışma

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Abstract

Aim: Influenza like illnesses (ILI) are the most prevalent reason for unnecessary antibiotic prescribing. Our aim was to evaluate the rapid antigen test (RAT) positivity with drug prescribing and clinical symptoms for ILI which is also a first report for Turkey.

Material and Methods: From September 2015 to June 2017, 1200 patients with ILI were included in this study. Nasopharyngeal swabs were taken from all enrolled patients. Antigen test was used for rapid detection of Influenza A/B virus, and the results were compared with clinical manifestations and drug prescriptions.

Results: RAT results were positive in 414 (34.5%) of 1200 patients. Fever (984 patients/82%), cough (727 patients/60.6%) and weakness (270 patients/22.5%) were common complaints. 371 (89.6%) out of 414 RAT positive patients had fever (p<0.01). 174 (42%) out of 414 RAT positive patients were medicated with antivirals (p<0.01). In addition, 516 (65.6%) out of 786 RAT negative patients were medicated with only antibacterial (p<0.01).

Conclusion: Our results supported a positive RAT test has an improving effect on the unnecessary antibiotic prescribing. However, in Turkey the prevalence of antibiotic prescription rates are still very high. Therefore we suggest that, RAT can be used effectively to reduce antibiotic usage when a quick decision is necessary.

Keywords: Influenza like illness; drug prescribing; RAT; clinical symptoms

Öz

Amaç: Influenza benzeri hastalıklar (ILI) akılcı olmayan antibiyotik kullanımının en sık sebeplerindendir. Bu çalışmadaki amacımız, Türkiye'den ilk bildirim olarak hızlı antijen testi (RAT) pozitifliğinin ilaç reçetelendirilmesi ve klinik belirtiler ile ilişkisini incelemektir.

Gereç ve Yöntemler: Eylül 2015-Haziran 2017 tarihleri arasında ILI tanısı almış 1200 hasta bu araştırma kapsamında değerlendirilmiştir. Tüm hastalardan nazofarenks sürüntüleri alınmış ve Influenza A/B tanısı amacıyla RAT ile incelenmiştir. Elde edilen sonuçlar, hastaların klinik durumları ve reçetelendirilmiş ilaçlar ile karşılaştırılarak değerlendirilmiştir.

Bulgular: RAT sonuçlarına göre 1200 ILI hastasının 414'ü (%34,5) Influenza A/B pozitif bulunmuştur. ILI tanısı alan hastalarda en sık görülen belirtiler ateş (984 hasta-%82), öksürük (727 hasta-%60,6) ve halsizlik (270 hasta-%22,5) olarak saptanmıştır. 414 RAT pozitif saptanan hastanın 371'inde (%89,6) ateş en sık saptanan belirti olmuştur (p<0,01). Bunun yanısıra 786 RAT negatif hastanın 516'sına (%65,6) sadece antibakteriyel ilaç reçete verilmiştir (p<0,01).

Sonuç: Sonuçlarımız RAT pozitifliğinin gereksiz antibiyotik reçetelendirilmesi üzerine olumlu bir etkiye sahip olduğunu göstermiştir. Buna rağmen Türkiye'de klinisyenlerin antibiyotik reçetelendirme oranları yüksektir. Sonuç olarak çalışmamız influenza tanısına hızla karar verilmesi gereken durumlarda RAT kullanımının gereksiz antibiyotik reçetelendirilme oranlarını düşüreceğini göstermiştir.

Anahtar kelimeler: influenza benzeri hastalık; ilaç reçetelendirilmesi; RAT; klinik belirtiler

Introduction

Influenza like illnesses (ILI) are known as causing serious acute respiratory tract infections show up every year as outbreaks and occasional pandemics [1, 2]. The most important clinical sign of ILI is reported as sudden onset of fever (≥37.8°C), accompanying with at least one of the symptoms such as myalgia, sore throat, frontal headache, chest pain and cough [3, 4]. Although Influenza types A and B are known to be predominantly responsible from these symptoms, other viruses (Human rhinovirus, Human adenovirus, Respiratory syncytial viruses, Human enterovirus, Para influenza viruses, Human bocavirus, Human coronavirus types) and bacteria (*Mycoplasma pneumoniae, Chlamydophila pneumoniae, Streptococcus pneumoniae, Legionella pneumophila*) can also be responsible from ILI. Diagnosis of ILI is clinically difficult [5-9]. According to data of World Health Organization (WHO) Global Influenza Surveillance and Response System (GISRS) published in May-2017, only 9% of ILI patients were diagnosed with influenza [10]. As mentioned above, symptoms of influenza infection are similar with other respiratory pathogens and clinical manifestations for true diagnosis of influenza infections are limited [11]. On the other hand, the diagnosis of influenza infections is critical and important for proper, early clinical patient management and isolation if needed [12-13]. Especially the risk groups for ILI cause an expansion on epidemic outbreaks and workforce loss which may generate a dramatic impact economically [14]. Treatment is also another important aspect during influenza epidemics; because it should begin within the first 48 hours following symptom onset, to provide some benefits especially for hospitalized patients [15-17].

For this reason rapid, easy and effective laboratory diagnostic tests may avoid inappropriate antibiotic prescription, which also leads the proper usage of antivirals and decreasing of nosocomial transmission as well [18]. Thus more cheaper, easier and less time consuming alternative tests are frequently preferred, such as rapid antigen detection tests [19, 20]. Although WHO declared some important clues for using of RAT for ILI diagnosis. Such as:

-During influenza outbreak or at the start of influenza season using rapid tests may affect clinical decisions and contribute to clinical awareness.

-Clinical evaluation and geographic surveillance data should be also considered in the first examination [20].

As we all know that the unnecessarily and overconsumption of antibiotics cause widely spreading of antibiotic resistance. Despite all limitations from ministry of health, irrational usage of antibiotics is very common especially during the treatment of ILI in Turkey; and according to data of Drug Industry Employers' Association, antibiotics were the mostly consumed drugs (12.3%) [21].

In this paper we aimed to evaluate the relation of RAT results with drug prescribing and clinical symptoms for ILI which is also a first report for Turkey.

Material and Methods

Clinical material

The patients suffering from influenza-like symptoms, who were administered to Istanbul Yeni Yuzyil Gaziosmanpasa (GOP) Hospital from September 2015 through June 2017 were included. Patients suffering from influenza-like symptoms (fever of greater than 37.8°C, cough, myalgia, congestion) in the absence of another cause were examined for influenza A/B infection. Nasopharyngeal swab samples were taken from all patients who have complaints given above. We also investigate the demographic data (age, symptoms during admission to hospital, hospitalized/non-hospitalized and prescriptions) from electronic patient files retrospectively. For rapid detection of Influenza A/B virus, SD BIOLINE Influenza antigen test (manufactured by Standard Diagnostics, INC. Korea) was used. Therefore convenience of rapid test results and prescribed drugs (antiviral, antibacterial, antifebrile, decongestant) by clinicians were also evaluated.

Rapid Detection of Influenza A/B

Influenza virus specific monoclonal antibodies are used to detect Influenza Antigen. SD Bioline test gives result within 15 to 30 minutes and is able to detect both Influenza A and B viruses (not subtypes of Influenza A). The test was performed according to the manufacturer's instructions. All specimens were placed in a tube containing an extraction agent provided by kit content. The positive result was determined by test line showing a color switching (pink to purple) in the A or B region with the presence of a control line [22]. According to the producing company, the overall sensitivity and specificity of the SD Bioline test have been reported as 91.8% % and 99.0 % respectively, for the influenza A/B virus antigen [23]. In our study the test was done by paramedics, according to the manufacturer's guidelines and its results were promptly communicated to the physician.

Statistical analysis

Regarding the statistical analyses, Chi-Squared Test, Chi-Squared Test with Yates Continuity Correction and Fisher's Exact Test were used to compare two observed proportions. As the statistical analyses for two population proportions is used in order to understand whether two populations significantly differ in terms of some single characteristic or not. All statistical tests were two-sided, and p values lower than 0.05 were considered to be statistically significant.

Results

Relationship between RAT results and clinical symptoms

A total of 1200 patients (55.8% children and 44.2% adult) suffering from influenza-like symptoms administrated to GOP hospital during the mentioned period. Ages of adult study group ranged from 16 to 98 years (mean age: 40.37±15.78) while pediatric study group ranged from one month to 17 years (mean age: 4.99±3.38). Adult patients included 244 males (46%) and 287 females (54%), while pediatric patients included 351 males (52.5%) and 318 females (47.5%). Distribution of RAT results according to age groups and Influenza types are shown in Table 1. 414 (34.5%) out of 1200 patients were found to have influenza infection according to rapid antigen test (RAT), and 268 of them (64.7%) were pediatric patients. 935 (77.9%) out of 1200 patients were treated without hospitalization, which 324 (34.7%) of them were found to be positive according to RAT result. 313 (75.6%) of RAT positive patients were shown to be infected with type A (Table 1).

Table 1. Influenza RAT results.			
Influenza RAT results	**Pediatric patients n=669 (%)**	**Adult patients n=531 (%)**	**Total n=1200 (%)**
Influenza positive	268 (40.1)	146 (27.5)	414 (34.5)
Influenza A positive	200 (29.9)	113 (21.3)	313 (26.1)
Influenza B positive	68 (10.2)	33 (6.2)	101 (8.4)
Influenza negative	401 (59.9)	385 (72.5)	786 (65.5)

According to our findings, fever (82%), cough (60.6%) and weakness (22.5%) were the most frequent symptom (Table 2). Among the most prevalent symptoms, only fever was found to be related with positive RAT result. 371 (89.6%) out of 414 RAT positive group were shown to have fever which was statistically significant (p <0.01) (Table 2).

Table 2. Symptoms, type of clinical observation and drug choice according to RAT results

	Pediatric patients (n=669)			Adult patients (n=531)			Total (n=1200)		
	Positive n=268 (%)	Negative n=401 (%)	p	Positive n=146 (%)	Negative n=385 (%)	p	Positive n=414 (%)	Negative n=786 (%)	p
Fever	256 (95.5)	366 (91.3)	0.092	115 (78.8)	247 (64.2)	0.003**	371 (89.6)	613 (78)	0.001**
Weakness	55 (20.5)	66 (16.5)	0.181	47 (32.2)	102 (26.5)	0.107	102 (24.6)	168 (21.4)	0.164
Headache	5 (1.9)	6 (1.5)	0.762	22 (15.1)	56 (14.5)	0.263	27 (6.5)	62 (7.9)	0.270
Myalgia	4 (1.5)	4 (1.0)	0.720	45 (30.8)	92 (23.9)	0.066	49 (11.8)	96 (12.2)	0.381
Cough	164 (61.2)	243 (60.6)	0.877	92 (63.0)	228 (59.2)	0.695	256 (61.8)	471 (59.9)	0.813
Sore throat	13 (4.9)	27 (6.7)	0.401	43 (29.5)	113 (29.4)	0.266	56 (13.5)	140 (17.8)	0.065
Hospitalized patients	84 (31.3)	131 (32.7)	0.719	6 (4.1)	44 (11.4)	0.016*	90 (21.7)	175 (22.3)	0.835
Only antiviral	111 (41.4)	3 (0.7)	0.001**	63 (43.2)	11 (2.9)	0.001**	174 (42)	14 (1.8)	0.001**
Only antibacterial	52 (19.4)	278 (69.3)	0.001**	20 (13.7)	238 (61.8)	0.001**	72 (17.4)	516 (65.6)	0.001**
Combination of antivirals and anti-bacterial	48 (17.9)	8 (2.0)	0.001**	46 (31.5)	10 (2.6)	0.001**	94 (22.7)	18 (2.3)	0.001**
Only anti-symptomatic therapy	57 (21.3)	112 (27.9)	0.052	17 (11.6)	126 (32.7)	0.001**	74 (17.9)	238 (30.3)	0.001**
Total Antiviral	159 (59.3)	11 (2.7)	0.001**	109 (74.7)	21 (5.5)	0.001**	268 (64.7)	32 (4.1)	0.001**
Total Antibacterial	100 (37.3)	286 (71.3)	0.001**	66 (45.2)	248 (64.6)	0.001**	166 (40.1)	534 (67.9)	0.001**
*p<0.05 **p<0.01									

Relationship between RAT results and drugs prescribed

It has been shown that 174 (42%) out of 414 RAT positive patients were medicated with only antivirals and in contrast with that, 516 (65.6%) out of 786 RAT negative patients were medicated with only antibacterial. Besides 94 (22.7%) RAT positive patients got both antiviral and antibacterial prescription. The relations of prescription content and RAT results for these three groups in both pediatric and adult groups were revealed as statistically significant (p<0.01) (Figure 1). In a total of 786 RAT negative patients, 238 (30.3%) of them treated with only anti-symptomatic drugs, which was also statistically significant (p <0.01) (Table 2).

Discussion

The rapid diagnosis of influenza infections is essential for early treatment and patient management. According to our knowledge, this is the first report which describes the utility of Influenza rapid antigen detection method on rational drug usage in Turkey. It is well known that the causative agents of upper or lower respiratory tract infections are cannot be distinguishable according to the early clinical signs which are defined as "influenza-like illness". According to the data of reference laboratories, the confidence of RAT has become a contradictive issue because of their susceptibility and specificity. The Centers for Disease Control and Prevention (CDC) reported that, during relatively low influenza period, the RAT has low positive predictive value. Therefore it has

been suggested that in the case of an critical decision, the RAT result should be confirmed [24]. However, WHO reported that RAT results should be regarded in case of rapid diagnosis and treatment are needed during the Influenza epidemics [20].

In the present study, in a total of 1200 cases, 414 (34.5%) of them were confirmed as influenza. It is well known that detection of some certain symptoms is associated with enhanced diagnostic accuracy. One of them is fever, which was observed in 89.6 % of 414 influenza RAT positive patients. Therefore our results showed that, there is a correlation between fever and RAT positivity. This result corroborates with previous data from United States, Japan, Mexico and China which shows the significant association between fever and influenza positivity [25, 26]. Monto et al. (2000) pointed out that "cough and fever" were the two best indicators and had positive predictive value (79%) for culture-proven influenza during the period of influenza circulating in the community [8]. D'Heilly et al. (2008) reported that "fever and cough" were common symptoms among individuals who have laboratory-confirmed influenza. Thus they suggested that "cough and fever" are 2.5 fold greater indicators for influenza infection [27]. Ciblak et al. (2009) reported that cough was the common symptom (68.7%) followed by fever >38^{0}C (62.5%) in their study from Turkey [28]. In the present study, clinical signs apart from fever were not found to be correlated with RAT results and the incidence of weakness (102 patients), headache (27 patients), myalgia

(49 patients) and throat ache (56 patients) were lower than previously reported [8, 29]. These results proved that clinical signs mentioned, may be associated with any respiratory tract infectious agents which are very difficult to identify.

Another point of seasonal influenza infection is to decide if the patient should be hospitalized or not. It is well known that patients with chronic illnesses (cardiovascular, renal, liver, pulmonary, diabetes and immunosuppression) have >30-fold increase in risk of hospitalization and death. Oxygen/ ventilator support, prolonged hospitalizations could be needed to achieve the truly patient management and prevent serious complications [30-32]. Although Bonner et al. (2003) suggested that RAT results are useful criteria for guiding clinical management decisions; in the present study, only 90 (21.7%) out of 414 RAT positive patients were hospitalized which 84 (31.3) of them were pediatric patients [12]. We assume that the reason for the hospitalization rates is because the hospital is a private medical center therefore patients and their relatives have economic concerns. In contrast with the present study, Castilla et al. (2016) reported that, hospitalized cases were more frequently aged 70 years or older (%61) who had major chronic conditions rate of 82% [33].

Another important result from the present study is related with rates of influenza types. According to data from public health institution of Turkey, in a total of 957 patients with acute respiratory tract infections, 215 (22.5%) of them were found to be influenza positive which 70% of them were type A [10]. Among the 414 RAT positive patients, type A was found to be more frequent (313 patients) which is consistent with (75.6%) previous results from Turkey (34). Another study conducted by Lee et al (2017) showed [35] that the prevalence of type A was found as 71.5% which is also lower than previous studies [30, 36, 37]. The reason of the difference in the prevalence of influenza subtypes could depend on the characteristics of study groups and the type of testing methods used (RT-PCR, RAT, cell culture, antibody detection).

The essential objective of the present study was to investigate the influenza RAT on rational drug prescription by clinicians. Therefore we also observed the content of prescriptions. In the present study, 300 (25%) out of total 1200 patients were prescribed antivirals, which only 268 (22.3%) of them were RAT positive while 32 (2.6%) were medicated with antivirals despite negative RAT results. Therefore it has been demonstrated that, clinicians may not always come to a decision according to RAT results because of their low susceptibility and specificity

ratios. Stein et al. (2005) suggested that during the influenza epidemics, the administrations of antiviral therapy may be appropriate to whom have both cough and fever [38]. Another study focusing on frequency of antiviral and antibacterial usage has been shown that, 91% of RAT positive patients with ILI symptoms received antiviral therapy [27]. Duman et al. (2013) reported that antiviral therapy was started 82.6% of their RAT positive patients and 56.8% of negative patients in the pediatric emergency department [39]. They also suggested that the patient's clinical manifestations and RAT results played a role to decide for treatment initiation. Therefore it has been estimated that, RAT results could be one of an effective indicator for reducing antibiotic usage.

As we know, usage of antibacterial drugs are not recommended for ILI especially during the influenza period. Despite all these suggestions the antibiotic prescriptions are shown to be very high in the present study. Moreover according to a cross-national database study of WHO in 2014, Turkey has been defined as the country which has the highest ratios of penicilins, cephalosporins and macrolides usage in all around the Europe [40]. According to "Rational antibiotic usage in human and animal health and antibiotic resistivity report of TUBA (Science Academy of Turkey), the insufficiencies of public health literacy and curriculum of medical schools on rational antibiotic usage, defects of social security institution and limitations on extensive investigations to determine the causative agents of ILI depending on different geographic regions are the main reasons of high antibiotic usage rates in Turkey [41].

It has been revealed that 700 (58%) of ILI diagnosed patients (386 pediatric / 314 adult population) were medicated with antibacterial drugs (only antibacterial and/or combined with antiviral drugs) which 76% (534 patients) of them were RAT negative and 24% of them (166 patients) were RAT positive. This results at least show that a positive RAT test has a improving effect on the unnecessary antibiotic prescribing. Even the frequency of antibiotic usage could be perceived as very high in GOP hospital, these ratios were lower than previous studies [27, 30, 42]. In relation to these, Canavaggio et al. (2017) reported that, some febrile ILI patients who were clinically pre-diagnosed in the emergency could not be confirmed with real-time PCR results or it was not possible to exclude bacterial co-infection [6].

Apart from all these significant relations mentioned in the present study, it has several potential limitations as well. We did not collect information about our patients' medical record

such as whom has chronic diseases, whom vaccinated, whom co-infected both with bacteria and influenza and duration of illness. We also could not compare RAT results with a reference test (cell culture or RT-PCR). It could also be interesting to observe the data about time from illness onset to specimen collection and source of the respiratory specimen, viral load, shedding, and discrimination of other possible etiologies (other viruses and bacteria).

Our results have shown that, even RAT results could not be confirmed with a reference test in the present study, it can still provide a rapid confirmation for clinical diagnosis which can lead a true treatment decisions such as possible prophylactic treatment of unvaccinated risk groups, reduce the infection rates of hospitalized patients, where there is a high risk of transmission and antibiotic usage. As a conclusion we would like to emphasize that, in Turkey the prevalence of antibiotic prescription rates are still very high. Therefore it seems that RAT can be used as an effective test for reducing of unnecessarily antibiotic prescription.

Declaration of conflict of interest

Acknowledgments

Ethical approval

Has been provided from Istanbul Yeni Yuzyil University Medical Faculty Research Ethics Committee. Meeting Date: 04.05.2017; No. 10.05.2017/026

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