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Association of clinical characteristics of patients presenting with influenza like illness or severe acute respiratory illness with development of acute respiratory distress syndrome

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Abstract

Clinical judgement and suspicion of influenza based on signs and symptoms of influenza-like illness and severe acute respiratory illness are critical for better patient outcome. Whether clinical characteristics of patients are associated with the development of acute respiratory distress syndrome was the aim of this study. We included all patients (n=37) presenting with influenza like illness (ILI) or severe acute respiratory illness (SARI) to a tertiary care hospital in northwest Pakistan during December 2015 until the end of January 2016. Each patient was assessed for signs and symptoms, clinical features, treatment, complications and outcome of ILI and SARI. Throat or nasopharyngeal swabs were obtained from 36 patient and analyzed for the presence of Influenza virus by quantitative PCR. Patients presenting with ILI or SARI were febrile ($p<0.001$, one sample *t*-test), significantly tachypneic ($p<0.001$) and had critically lower oxygen saturation ($p<0.001$). Nasal congestion at presentation ($p=0.006$, chi-square test for association) and infiltrates on chest radiographs ($p=0.025$) were significantly associated with acute respiratory distress syndrome. Likelihood of the occurrence of ARDS was significantly increased with decrease in oxygen saturation (Odds ratio; 0.75, 95% CI; 0.46, 1.21, $p=0.048$) and marginally significantly increased in lower age (Odds ratio; 0.82, 95% CI; 0.58, 1.15, $p=0.055$) and higher white cell count (Odds ratio; 1.001, 95% CI; 0.99, 1.002, $p=0.054$). The presence of Influenza type A/H1N1pdm09 strains was confirmed in 7/11 patients. However no significant difference was observed in the clinical features and complications of PCR positive and negative patients. Clinical signs and symptoms of influenza-like illness or severe acute respiratory illness significantly predict the development of complications irrespective of the positivity or negativity of laboratory qPCR reports.

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Introduction

Influenza, commonly known as flu, is a highly contagious acute respiratory viral disease. The spectrum of disease range from mild to severe illness and even death. Almost every year, seasonal flu epidemics are mainly caused by human Influenza A and B viruses [1]. In recent years, a global outbreak of H1N1 swine flu took its origin from a pig farm in Mexico in April 2009 [2], gradually spreading towards Southern hemisphere and underdeveloped regions of the world causing laboratory confirmed cases of pandemic influenza H1N1 pdm/09 in 209 countries and causing a death toll around 17,000 people [2]. Recently, as of February 2016, more than 250 laboratory confirmed H1N1 pdm/09 cases have been reported from Caribbean islands and South America [3]. Out of more than 155 thousand specimens collected from 98 countries by World Health Organization in the month of February 2016, approximately 30% tested positive for influenza viruses, of which 80% were influenza A, mainly (H1N1)pdm/09 [3].

Patients with H1N1 generally present with influenza like illness (ILI; as defined by WHO as those with sudden onset of fever (>38°C) and cough/sore throat within seven days of onset) or severe acute respiratory illness (SARI; defined as patients with sudden onset of fever (>38°C), cough/sore throat that required hospital admission within 7 days) [4]. Since the detection of first laboratory confirmed case of swine flu in Pakistan on August 10th 2009 [5], sporadic cases are reported on yearly basis. This winter 2015-2016 the country had an epidemic of H1N1 flu with more than 240 cases confirmed until February 2016 [6]. In Pakistan, clinical specimens obtained from patients presenting with ILI or SARI are usually reported after 10-12 days for logistic reasons and lack of facilities for quantitative determination of Influenza virus in the city. On the other hand, the infectivity period of patient presenting with these symptoms is from one day before the onset of symptoms and until 3 days after the onset of symptoms [7]. Hence, isolation and definitive treatment of patient after qPCR confirmation is expected to significantly increase the morbidity, mortality and cross-infection. In this scenario, clinical judgement and suspicion is critical for the better primary and secondary prevention of this disease. Therefore, the aim of this study was to evaluate the magnitude and clinical characteristics of patients presenting with influenza like illness or severe acute respiratory illness admitted to tertiary care hospitals in northwest Pakistan between December 2015 and February 2016.

Materials and Methods

Study design

This was a prospective observational study of all 37 patients (females, n=25, males; n=12) presenting with severe acute respiratory illness (SARI) or Influenza like illness (ILI) to a tertiary care hospital (Government Lady Reading Hospital) in Peshawar Khyber Pakhtunkhwa Pakistan between December 2015 until the end of January 2016. Initially patients presented to various departments (including Pulmonology, Medicine, and intensive care), they were eventually isolated in Pulmonology department for further management.

Methods

Each patient was assessed according to the standard protocols issued by the National Institute of Health (NIH) Islamabad. Briefly, each patient was assessed for signs and symptoms of ILI and SARI, history of contact with sources of influenza, clinical complications, and outcomes of disease during the process of treatment in hospital. Throat or nasopharyngeal swabs were obtained from 36 patients and sent to NIH central laboratory Islamabad for quantitative PCR for Influenza virus. All patients received standard hospital care as per protocols. Informed oral consent was obtained from each patient. The study was approved by the Ethics committee of Khyber Medical University Peshawar and Government Lady Reading Hospital Peshawar.

Analysis

Data was organized in Microsoft Excel 2013 (Microsoft®) and then analyzed using Minitab ver. 17 (Minitab® Inc., State College, PA, USA). Continuous data was expressed as mean and standard deviation, while categorical data was expressed as counts and percentage. One sample t-test was used to calculate the difference between body temperature, respiratory rate, oxygen saturation, and white cell count and their standard cut-off values. Binary logistic regression analysis was used to assess the association of the occurrence of acute respiratory distress syndrome with age, respiratory rate, body temperature, white cell count, and oxygen saturation. P-value of less than 0.05 was considered significant.

Results

All patients (n=37) with mean (±SD) age of 40.46 (±15.27) years presenting with influenza like illness (ILI) or severe acute respiratory illness (SARI) were included in this study. Of these 25 (67.57%) were females and 12 (32.43%) were males. Most of these patients were from Khyber Pakhtunkhwa [25 (67.57%)], while the rest were belonging to federally administered tribal areas (11/37) and Afghanistan (1/37). All women presenting with symptoms were house wives [24 (64.8%)], the rest included drivers [3 (8.18%)], students [2 (5.41)], painter, security guard and shopkeeper [1 (2.7%) each], and other professions [3 (13.5%)]. Most of the patients were inpatients (35/37, 94.59%) presenting to pulmonology [31 (86.11)], Medicine [2 (5.55%)], or other departments such as intensive care unit, high dependency unit or other wards [4 (11.11%)].

Although most of the patients presented with cough 36(97.3%) and fever (temperature >38°C) [32(86.48%)], index of suspicion of an influenza infection was very low [1 (2.7%)]. Based on the standard criteria for SARI case definition, 86% patients were labeled as having severe acute respiratory illness. Very few patients [3 (8.11%)] gave a history of contact with probable sources of influenza.

Apart from fever and cough, patients mainly presented with shortness of breath, sore throat, abnormal breath sounds, wheezing and nasal congestion (Table 1). Patients presenting with ILI or SARI were

Table 1. Clinical characteristics of patients presenting with influenza like illness or severe acute respiratory illness.

Characteristic	Total N (%)	Developed ARDS N (%)	No ARDS N (%)	p-value*
Findings on chest radiograph				
Normal chest X-ray	5(13.51)	1(20)	4(80)	0.508
Infiltrate	22(59.46)	4(18.18)	18(81.82)	0.025
Consolidation	27(72.97)	10(37.04)	17(36.96)	0.312
Cavitations	21(56.76)	7(33.33)	14(66.66)	0.893
Opacities	24(64.86)	9(37.5)	15(62.5)	0.363
Effusion	1(2.70)	0(0.00)	1(100)	NC
Pneumatocele	2(5.41)	0(0.00)	2(100)	NC
Bronchopneumonia patches	11(29.73)	6(54.54)	5(45.45)	0.066
Clinical signs and symptoms				
Cough	36(97.3)	11(91.67)	1(8.33)	NC
Fever	36(97.3)	11(91.67)	1(8.33)	NC
Nasal congestion	24(64.86)	4(16.66)	20(83.33)	0.006
Sore throat	30(81.08)	9(30)	21(70)	0.520
Wheezing	28(75.68)	7(25)	21(75)	0.096
Tachypnea	10(27.03)	5(50)	5(50)	0.173
Abnormal breath sounds	30(81.08)	9(30)	21(70)	0.520
Hemoptysis	5(13.51)	2(40)	3(60)	0.702
Sputum production	13(35.14)	4(30.76)	9(69.24)	0.873
Chest pain	30(81.08)	9(30)	21(70)	0.513
Shortness of breath	32(86.49)	10(31.25)	22(68.57)	0.702
Index of suspicion of avian influenza	1(2.70)	1(8.33)	0 (0.00)	NC
History of contact with probable sources of influenza	3(8.11)	2(16.66)	1(8.33)	NC

*χ^2-test for association; ARDS: acute respiratory distress syndrome; NC: value not computable due to low number.

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febrile (p<0.001, one sample *t*-test), tachypneic (p<0.001, one sample *t*-test) and had critically lower oxygen saturation (p<0.001, one sample *t*-test) (Table 2). We performed Chi-square test to assess whether a particular mode of clinical presentation was associated with the development of ARDS and observed that nasal congestion (p=0.006) was associated with the subsequent development of ARDS. Antibiotics were used by 32 (86.24%) patients prior to admission, however use of antivirals was not reported by any of the patient. Significantly higher number of patients who did not develop ARDS used antibiotics prior to their presentation (No ARDS; 24/25 *vs* ARDS; 8/12, p=0.018, χ^2-test). Chest radiograph showed abnormal findings in 32 (86.49%) patients, mainly consolidations, opacities, infiltrations or cavitations (Table 1). Infiltration seen on chest X-ray was significantly associated with the development of ARDS (p=0.025, χ^2-test). Majority of patients [32 (86.49%)] developed one or more than one complications as a result of the disease, of which 28 (75.68%) patients developed pneumonia, 12(32.43%) patients developed ARDS and 2(5.41%) patients eventually progressed to respiratory failure. Presence of cough (p=0.038, Fisher's exact test), nasal congestion (p=0.023, χ^2-test), wheezing (p=0.012, χ^2-test), and chest pain (p=0.001, χ^2-test) was significantly associated with the occurrence of pneumonia. Oxygen therapy was required for 29 (78.38%) patients and 12 (32.43%) patients required ventilation. Three patients (8.11%) died of the complications and the rest were discharged.

Whether the occurrence of acute respiratory distress syndrome is associated with age, temperature, respiratory rate, oxygen saturation and white cell count, binary logistic regression analysis was used considering the occurrence of ARDS as an event (Table 3). Likelihood of the occurrence of ARDS was significantly increased with a decrease in oxygen saturation (Odds ratio: 0.75, 95%; CI: 0.46, 1.21; p=0.048) and marginally significantly increased with decreasing age (Odds ratio: 0.82, 95%; CI: 0.58, 1.15; p=0.055) and higher white cell count (Odds ratio: 1.001, 95%; CI: 0.99, 1.002; p=0.054).

Based on the presentation of patients, throat swabs were obtained from 34 (91.89%) patients and nasopharyngeal swabs from two patients. Out of 36 samples sent for qPCR analysis, reports of only 11/36 (30.5%) samples were available at the time of conclusion of this study. These results confirmed the presence of Influenza type A/H1N1pdm09 strains in 7 (63.63%) patients. However, no significant difference was observed in the clinical features and complications of PCR positive and negative patients.

Discussion

Our study suggests that patients presenting with cough, nasal congestion, wheezing, and chest pain are likely to develop complications of respiratory tract infections such as pneumonia and should be suspected and investigated for influenza A (H1N1) infection. Furthermore, no difference in the severity of symptoms between PCR positive and PCR negative patients indicate that treatment may be considered in the lines of Influenza A infections by the attending physician in the light of current influenza epidemic. This is supported by previous studies which showed that clinical characteristics of patients presenting with ILI or SARI were significantly associated with the presence of influenza A(H1N1)pdm09 [8,9].

In line with previous evidence [8,10-12], cough and fever were the cardinal symptoms of patients admitted to the pulmonology department. Similarly, abnormal radiological findings were reported in majority of patients in our study. Patchy infiltration, consolidations, and pleural effusions have also been reported previously [10]. Unlike other studies [11], our patients did not report diarrhoea. Occurrence of diarrhoea is common in H1N1, mainly in children and also in adults during pandemics. However, it is less commonly reported in seasonal influenza. Children are also more likely to develop complications of influenza irrespective of the severity of symptoms [11]. Our cohort did not include children, however a significant association of the development of ARDS with decreasing age reaffirms this notion.

Evidence of exposure or contact with sources of influenza virus was not reported by majority of patients in this study indicating that the primary source may have been from the animals to which humans are not resistant due to the absence of innate re-acquired immunity to the genetically re-assorted influenza virus. Animal and birds have their own set of influenza viruses that cause flu outbreaks in respective species. Although the swine flu virus (swine influenza A virus) is specie specific but zoonotic jumps have been seen crossing the specie barrier from pigs to humans [7]. In this new host, the virus undergoes genetic re-assortment leading to the origin of a new hybrid variety of super-virus to which humans lacks both innate and acquired immunity. This subsequently spreads swiftly in human population, posing a threat in the form of Influenza pandemic [7]. Index of suspicion of H1N1 increases with history of contact of patient with probable sources. Women, especially house wives, in Pakistani culture spend most of their time in the house and are therefore less frequently exposed to the

Table 2. Clinical parameters of admitted patients.

Variable	Mean	Std. dev	p-value*
Temperature °C (n=37)	38.75	0.58	<0.001
Respiratory rate (per minute) (n=28)	31.82	6.83	<0.001
Oxygen saturation % (n=33)	81.09	10.98	<0.001
White cell count (n=19)	11321	8046	0.864

*One sample *t*-test: Std. dev: standard deviation.

Table 3. Binary logistic regression for the association of continuous predictors with the development of ARDS.

Variable	Odds ratio	95% CI	p-value
Age (years)	0.818	(0.5833, 1.1476)	0.055
Temperature (°C)	0.0001	(0.0000, 3242.1)	0.166
Respiratory rate (per minute)	0.989	(0.5220, 1.8729)	0.973
Oxygen saturation (%)	0.746	(0.4587, 1.2144)	0.053
White cell count	1.001	(0.9996, 1.0015)	0.048

CI: confidence interval.

sources of influenza unless a family member is infected. Surprisingly, majority of patients (67.5%) presenting with SARI in our study were house wives and our data does not show any history of contact with infected patients. Furthermore, women going out of their houses wear veils which reduces their chance of acquiring an infection. This finding needs to be investigated in further studies.

Approximately 32% of our patients developed acute respiratory distress syndrome (ARDS) and subsequently needed mechanical ventilation. Patients who had severe nasal congestion and infiltration on chest radiograph were more likely to develop ARDS. Similarly decrease in oxygen saturation, younger age, and higher white cell count was significantly associated with the development of ARDS. Given the pathogenesis of ARDS, the association of these signs and symptoms with ARDS is expected [13], however presentation of patients with these findings will specifically help attending physician to plan aggressive management of patient prior to the development of ARDS.

No significant difference in the severity of patients' symptoms based on RT-PCR positivity were noted, which indicates that the initial suspicion at the time of admission should be the guiding point for the attending physician on the lines of H1N1 suspected case. This should however be interpreted with caution as we do not know if the patients presented, and their swabs obtained, within 5-7 days after the onset of Influenza like symptoms. Evidence suggests that PCR positivity is doubtful after 5-7 days of active infection [7].

Reported death of fewer patients (3 out of 37 patients) in this study compared to previous studies [10,12] indicate that the use of antivirals and complementary antibiotics in ILI and SARI were effective and justified to reduce significant morbidity and mortality. Antiviral agents such as oral oseltamivir and inhaled zanamivir are associated with better disease outcomes, shorter duration of disease, and fewer rates of hospitalization in large meta-analyses [14]. However the quality of evidence available for these meta-analyses is limited and with low confidence of effect.

This study is not without limitations. As mentioned above, we did not have data regarding the duration between onset of ILI or SARI symptoms and presentation to the hospital. We also did not have RT-PCR reports for all patients limiting correlation of clinical signs and symptoms with confirmed presence of the virus.

In conclusion, clinical signs and symptoms of influenza like illness or severe acute respiratory illness significantly predict the development of complications irrespective of the positivity or negativity of laboratory PCR reports. It is recommended that these patients should be rigorously managed at presentation to prevent the development of complications and full blown respiratory disease.

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