International Journal of Infectious Diseases 16 (2012) e504–e507

Contents lists available at SciVerse ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Clinical characteristics of influenza A H1N1 versus other influenza-like illnesses amongst outpatients attending a university health center in Oman

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ARTICLE INFO

Article history:
Received 24 May 2011
Received in revised form 21 February 2012
Accepted 29 February 2012

Corresponding Editor: Jane Zuckerman, London, UK

Keywords:
H1N1
Real-time reverse transcriptase
Influenza-like illness
Clinical characteristic
Oman

SUMMARY

Objectives: To identify the clinical characteristics of outpatients with flu-like illnesses stratified by influenza A H1N1 status.
Methods: The study was conducted at the H1N1 staff clinic of Sultan Qaboos University Hospital in Muscat, Oman. The population consisted of university students and university/hospital staff and their family members. All adult patients who presented to the H1N1 clinic with an influenza-like illness over a 4-month period (from August until the end of November 2009) were included. Real-time reverse transcriptase (rRT) PCR was used for the diagnosis of H1N1 influenza. Demographic data, clinical signs and symptoms, history of exposure to H1N1, history of recent travel, and co-morbid conditions were documented. Analyses were conducted using univariate and multivariate statistical techniques.
Results: Out of the 2318 patients identified, 27% ($n = 616$) were positive for H1N1 influenza. The mean temperature in the H1N1-positive group was significantly higher than in the negative group (38.3 °C vs. 37.2 °C; $p < 0.001$). Proportions of patients who reported cough, sore throat, headache, myalgia, gastrointestinal symptoms, exposure to a confirmed case of H1N1, and a history of travel were significantly higher in the H1N1-positive group as compared to the swab-negative group. However, the multivariable logistic model identified only the following significant predictor variables of H1N1 infection: younger age, fever (≥37.8 °C), sore throat, myalgia, diarrhea, and exposure to a confirmed H1N1 case within the last 7 days.
Conclusions: This study provides useful data on the clinical characteristics of H1N1 influenza in a large outpatient population from the Middle East. Patients who tested positive for H1N1 were more likely to have fever, sore throat, diarrhea, and myalgia compared to those with other influenza-like illnesses.

1. Introduction

In late March 2009, an outbreak of influenza A H1N1 virus infection was detected in Mexico. The virus then spread rapidly to many other regions of the world.[1,2] In late April, the World Health Organization (WHO) announced the emergence of a novel influenza A virus, and in June 2009, the WHO raised its pandemic alert level to the highest level.[3] More than 214 countries, including the countries and territories of the Middle East, reported laboratory-confirmed cases of pandemic H1N1 influenza A.[4] The pandemic was declared to be over in August 2010.[5] The first confirmed case of H1N1 in Oman was reported in June 2009, and the total number of confirmed cases detected by the beginning of January 2010 was 7040 with 31 deaths.[6] As of November 2009, the total number of confirmed cases in the Eastern Mediterranean region (to which Oman belongs) was 22 689, and 137 of these cases had died.[7]

The spectrum of H1N1 influenza has been described to range from a non-febrile, mild upper respiratory tract illness to severe or fatal pneumonia.[8] The most commonly reported symptoms are cough, fever, sore throat, malaise, and headache.[8–10] The least commonly reported symptoms are nausea, vomiting and/or diarrhea.[8–10] The clinical diagnosis of an influenza infection is often elusive given its non-specific presentation. From a health perspective, differentiating between influenza and influenza-like illnesses (ILI) caused by other respiratory pathogens could be very valuable because of the availability of specific antiviral therapies,[11] the potential serious complications of this disease,

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1201-9712/$36.00 – see front matter
http://dx.doi.org/10.1016/j.ijid.2012.02.015

and the ability of influenza virus to cause epidemics and global pandemics.

There are currently several published studies[12–14] that have compared the clinical characteristics of patients affected by seasonal influenza and those presenting with ILI caused by other respiratory pathogens. As there are differences in socio-demographic and epidemiological trends between different countries, clinical characteristics and disease severity may differ among different populations. Therefore, we aimed to identify the differences in clinical characteristics between patients with an ILI who are negative for H1N1 and those who are positive for H1N1 in an outpatient Omani population.

2. Methods

We conducted a retrospective electronic chart review of all adult patients (≥17 years) who attended the H1N1 staff clinic at the health center of Sultan Qaboos University Hospital (SQUH). This is a government hospital located in the capital city of Muscat, Oman. We reviewed the charts of patients who were registered from August 1, 2009 to November 30, 2009, which was the time of the H1N1 epidemic in Oman. The H1N1 staff clinic is run by medical officers, family physicians, and family medicine residents. The study population consisted of university students and university/hospital staff and their family members. These included both Omanis and expatriates from all over the world. The university health center at SQUH is not open to the public; all non-eligible patients are routinely directed to the emergency department of the hospital.

All patients, with self-reported influenza-like symptoms including fever, cough, sore throat, headache, nasal symptoms, and myalgia, with or without documented fever, attended the H1N1 clinic. All patients with such symptoms were tested for H1N1. Two swabs were taken for each patient, one from nasopharynx and the other from the throat. Both swabs were collected in the same transport medium. An oropharyngeal swab was considered as an alternative to the nasopharyngeal swab in the case that the clinician failed to reach the nasopharynx. Real-time reverse transcriptase (rRT) PCR was used for the diagnosis of H1N1 influenza virus infection. The advantages of using this test include its ability to yield relatively rapid results and to differentiate between influenza types and subtypes.[15] The laboratory reported either positivity or negativity for H1N1. Other respiratory pathogens were not reported.

A data collection form was developed to include the following variables: age, gender, nationality (Omani vs. non-Omani), temperature in degrees Celsius, time from symptom onset to presentation in days, the presence of symptoms (sore throat, cough, nasal symptoms, headache, myalgia, nausea, vomiting, and diarrhea), the presence of co-morbid conditions (asthma, chronic obstructive pulmonary disease, interstitial lung disease, cardiovascular disease, diabetes, pregnancy, HIV, malignancy, and use of immunosuppressant drugs), a history of exposure to H1N1 within the last 7 days, a history of travel within the last 7 days, whether hospital admission was required or not, and the swab status.

This study was not funded. Ethical approval for the study was obtained from the Ethical Review Committee (ERC) of the College of Medicine and Health Sciences, Sultan Qaboos University.

2.1. Statistical analysis

Descriptive statistics were used to describe the data. For categorical variables, frequencies and percentages were reported. Differences between groups (H1N1 status, negative/positive) were analyzed using Pearson's Chi-square tests (or Fisher's exact tests for cells less than 5). For the variable temperature, the mean and standard deviation were used to present the data, while analysis was performed using the Student's *t*-test. For variables that were not normally distributed, medians and interquartile ranges (IQR) were used to describe the data, while the analyses were conducted using the Mann–Whitney test.

The associations between H1N1 and the various predictive demographic and clinical symptoms were assessed using multivariable logistic regression. The dependent outcome variable was H1N1 influenza, while the predictor variables were age, gender, nationality (Omani/non-Omani), fever (temperature ≥37.8 °C), sore throat, cough, headache, myalgia, vomiting, diarrhea, rhinorrhea, exposure to a confirmed H1N1 case within the last 7 days, and history of travel. The goodness-of-fit of the logistic model was examined using the Hosmer–Lemeshow goodness-of-fit statistic.[16] An a priori two-tailed level of significance was set at the 0.05 level. Statistical analyses were conducted using STATA version 12.0 (STATA Corp., College Station, TX, USA).

3. Results

In total, the electronic medical records of 2355 patients were reviewed. Patients with missing or incomplete information, or for whom an H1N1 swab could not be performed, were excluded from the study. There were 26 incomplete records, 11 in the H1N1-positive group and 15 in the swab-negative group; in an additional 11 cases, either a swab could not be taken or it was inadequate.

The comparison of demographic information, clinical signs and symptoms, underlying co-morbid conditions, exposure history, and travel history of the study participants from both groups are presented in Table 1. Out of 2318 patients, 1702 (73%) were negative for H1N1 influenza and 616 (27%) were positive for H1N1. The overall median age was 25 (IQR 21–34) years. The majority of the patients were Omanis (81%; $n = 1870$). Among the study participants, males constituted 53% of the swab-negative group and 57% of the H1N1-positive group. Approximately 28% of patients in the swab-negative group and 25% of patients in the H1N1-positive group were health care professionals. None of our patients required referral for hospitalization.

The mean temperature in the H1N1-positive group was significantly higher than that in the swab-negative group (38.3 °C vs. 37.2 °C; $p < 0.001$). Moreover, 78% of the patients in the H1N1-positive group had a temperature ≥37.8 °C compared to 16% in the swab-negative group ($p < 0.001$). The proportions of patients who reported cough, sore throat, headache, myalgia, gastrointestinal symptoms, exposure to a confirmed case of H1N1, and a history of travel were significantly higher in the H1N1-positive group as compared to the swab-negative group. No significant differences were found between the two groups with regard to the occurrence of co-morbid conditions or the time from symptom onset to presentation.

Utilizing the stepwise-backward elimination method, the multivariable logistic model (Table 2) demonstrated that significant variables included younger age, exposure to a confirmed H1N1 case, temperature ≥37.8 °C, sore throat, diarrhea, and myalgia.

4. Discussion

This observational study describes an outpatient population of 2318 symptomatic adults who visited H1N1 clinics during the 2009 H1N1 pandemic in Oman between August 1 and November 30, 2009. Almost a third (27%) of patients were found to be positive for H1N1. According to our findings, these patients were much more likely to report the following symptoms: fever, cough, sore throat, headache, myalgia, vomiting, and diarrhea. Furthermore, swab-positive patients had a significantly higher mean tempera-

Table 1
Demographic and clinical characteristics of the study cohort stratified by H1N1 status ($N = 2318$)[a]

Characteristic	All	H1N1 status		p-Value
		Negative ($n = 1702$; 73%)	Positive ($n = 616$; 27%)	
Demographic characteristics				
Age, years, median (IQR)	25 (21–34)	25 (21–34)	25 (21–33)	0.345
Male gender	1251 (54.0%)	900 (52.9%)	351 (57.0%)	0.080
Omani	1870 (80.7%)	1354 (79.6%)	516 (83.8%)	0.023
Exposure[b]	762 (32.9%)	487 (28.6%)	275 (44.6%)	<0.001
Travel	55 (2.4%)	31 (1.8%)	24 (3.9%)	0.004
Health care provider	633 (27.3%)	478 (28.1%)	155 (25.2%)	0.163
Clinical characteristics				
Temperature, °C, mean (± SD)	37.5 (± 0.8)	37.2 (± 0.6)	38.3 (± 0.8)	<0.001
Temperature ≥37.8 °C	743 (32.1%)	265 (15.6%)	478 (77.6%)	<0.001
Duration of symptoms, days, median (IQR)	2 (1–2)	2 (1–2)	2 (1–2)	0.939
Sore throat	1365 (58.9%)	864 (50.8%)	501 (81.3%)	<0.001
Cough	1702 (73.4%)	1200 (70.5%)	502 (81.5%)	<0.001
Nasal symptoms	1703 (73.5%)	1286 (75.6%)	417 (67.7%)	<0.001
Headache	460 (19.8%)	285 (16.7%)	175 (28.4%)	<0.001
Myalgia	612 (26.4%)	316 (18.6%)	296 (48.1%)	<0.001
Vomiting	120 (5.2%)	62 (3.6%)	58 (9.4%)	<0.001
Diarrhea	191 (8.2%)	79 (4.6%)	112 (18.2%)	<0.001
Co-morbidity				
Asthma	109 (4.7%)	86 (5.1%)	23 (3.7%)	0.185
Diabetes	44 (1.9%)	37 (2.2%)	7 (1.1%)	0.106
Pregnancy	53 (2.3%)	43 (2.5%)	10 (1.6%)	0.199
COPD	7 (0.3%)	5 (0.3%)	2 (0.3%)	1.000

IQR, interquartile range; SD, standard deviation; COPD, chronic obstructive pulmonary disease.
[a] Results are *n* (%), unless otherwise stated. Analyses were conducted using the Student's *t*-test, Mann–Whitney test, Pearson's Chi-square test, or Fisher's exact test, whenever appropriate.
[b] Exposure to a confirmed H1N1 case within the last 7 days.

ture. They were also much more likely to have been exposed to a suspected case of H1N1 and more likely to have a history of recent travel.

Fever and cough have been reported to be the two best predictive symptoms for influenza infection, particularly in elderly individuals.[12,17] These two key symptoms have also been described as the most common amongst H1N1-infected patients.[9,10,18,19] Another commonly reported symptom is sore throat.[9,20]

According to our results, 18% of H1N1 patients complained of diarrhea and 9% reported vomiting. These were the least commonly reported symptoms by our patients. The frequencies of both these symptoms were lower than those reported by Dawood et al. (25% for each symptom),[9] but higher than those reported in other studies.[21,22] In a comparison between patients infected with pandemic H1N1 (2009) influenza and those infected with seasonal influenza, Carcione et al. identified diarrhea as a significant variable distinguishing H1N1-infected patients.[13] However, a study from Singapore did not confirm the same finding.[23]

Our multivariate analyses identified the following significant variables: younger age, exposure to a confirmed case, temperature ≥37.8 °C, sore throat, diarrhea, and myalgia. The finding that H1N1 virus affects predominantly younger individuals has been reported by most of the previous studies.[9,20,21] The most likely reason for this finding is the cross-reactive immunity in older patients (age >60 years), which has arisen from their longer lifetime exposure to strains similar to that of the pandemic H1N1 virus.[24] Ong et al. reported that fever is a significant predictor of a laboratory diagnosis of H1N1.[12] In another study, age <65 years and cough were found to be independent predictors of pandemic H1N1 (2009) virus.[25] Results from studies testing various clinical models and case definitions that aim to identify patients with influenza based solely on clinical characteristics have been disappointing.[26–28] Studies have generally shown that ruling out influenza using clinical and contextual information is easier than ruling it in.[28,29] It has been suggested that other contextual information, such as the knowledge of an epidemic, is needed in order to improve the sensitivity of a clinical case definition.[28]

Our study has several limitations. The study population was not representative of a typical outpatient setting, since it consisted of only young and relatively healthy individuals and excluded children, elderly individuals, and patients with major co-morbid conditions. H1N1 cases may have been missed if the swab was not taken properly or obtained late in the course of the disease. It is not clear what respiratory pathogens were involved in our H1N1-negative group since no other respiratory pathogens except H1N1 were reported. As our patients were only seen in the outpatient

Table 2
Predictive symptoms of H1N1 in the study cohort using multivariable logistic regression ($N = 2318$)[a]

Predictor	AOR	95% CI	p-Value
Male	1.19	0.93–1.53	0. 158
Age	0.96	0.95–0.98	<0.001
Omani citizen	1.25	0.85–1.83	0.252
Temperature ≥37.8 °C	14.5	11.1–18.7	<0.001
Sore throat	1.90	1.44–2.52	<0.001
Cough	1.10	0.80–1.50	0.554
Headache	0.76	0.56–1.03	0.072
Myalgia	2.05	1.56–2.69	<0.001
Vomiting	1.49	0.86–2.58	0.158
Diarrhea	3.46	2.29–5.23	<0.001
Nasal symptoms	1.21	0.93–1.59	0.160
Exposure to a confirmed H1N1 case within the last 7 days	1.71	1.33–2.20	<0.001
Travel	1.69	0.82–3.50	0.156

AOR, adjusted odds ratio; CI, confidence interval.
[a] The final logistic model is statistically significant (likelihood ratio Chi-square (13) = 937.98; $p < 0.001$). The Hosmer–Lemeshow Chi-square statistic (a measure of the goodness-of-fit) was 5.72 and the *p*-value was 0.679. The model also had a C-index of 0.87 denoting good discriminatory ability. The pseudo R^2 was 35%. The model correctly classified 84% of the H1N1 cases.

setting, our results cannot be extrapolated to other clinical settings.

In summary, our study provides useful data on the clinical characteristics of the pandemic H1N1 (2009) virus in a large outpatient population from the Middle East. Our findings indicate that the clinical presentation of H1N1 infection can, to some extent, be distinguishable from that of an ILI caused by other pathogens, by the presence of the following predictor variables: younger age, high-grade fever, sore throat, myalgia, diarrhea, and a positive exposure history.

Acknowledgements

The authors would like to acknowledge all the staff of SQUH who worked directly or otherwise at the H1N1 clinic during the outbreak. The authors would also like to thank Meriel Carboni who proofread the manuscript for grammar before publication.

Funding: This study was not funded.

Conflict of interest: The authors have no conflict of interest (financial or otherwise) to report.

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