Brief Original Article

Clinical manifestations of pandemic (H1N1) 2009 in the ambulatory setting

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Abstract

Introduction: In June 2009, the World Health Organization declared an influenza pandemic associated with the pandemic (H1N1) 2009 strain. It was summer in the northern hemisphere, and therefore travelling and vacation time, which also provided an increased opportunity for the dissemination of respiratory diseases.

Methodology: We reviewed the paper case report forms from all the patients with influenza-like illnesses with nasopharyngeal samples submitted for laboratory diagnosis of pandemic (H1N1) 2009 infection during the first wave of pandemic influenza that occurred between June and August 2009, in the central region of Portugal.

Results: From all the patients with influenza-like illnesses, one third was found positive for pandemic (H1N1) 2009. Individuals under the age of 29 (75%) were the most affected.

Most of the patients (91%) presented with fever. A group of symptoms were positively correlated with the probability of pandemic (H1N1) 2009 infection: cough, epistaxis, lack of dyspnea or vomiting, fever, headache and myalgia.

Conclusions: During the first wave of the pandemic influenza, young individuals were the most affected, and in the ambulatory setting, presentation was of a mild febrile illness without complications.

Key words: pandemic; H1N1; influenza; 2009; manifestations

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Introduction

The media reported several outbreaks of influenza-like illness in Mexico occurring in different regions of the country in April 2009 [1]. Later, the first confirmed human cases of swine-origin influenza A (H1N1) virus infection in the southern states of Texas and California, close to the Mexican border, were described in the United States of America [2].

A rapid spread of the infection occurred thereafter reaching different regions of the world and documentation of human-to-human transmission of the virus in at least three countries in two of the six world regions defined by the World Health Organization (WHO) prompted the organization to raise the pandemic level from 5 to 6 and to declare an influenza pandemic [3].

Influenza pandemics have been known to cause multiple waves of morbidity and mortality over a few months or years although the cause of the wave behaviour of influenza pandemics is not precisely understood.

In the northern hemisphere, the pandemic developed during the spring and summer months, a time when many people are travelling and vacationing, which therefore also presented an increased opportunity for the dissemination of respiratory diseases.

This study analyzed the clinical manifestations of influenza-like illnesses with samples submitted for laboratorial diagnosis of pandemic (H1N1) 2009 virus infection in the ambulatory setting during the first wave of pandemic influenza in the central region of Portugal.

Methodology

Oropharyngeal and nasopharyngeal swabs were collected and submitted for laboratory diagnosis of pandemic (H1N1) 2009 virus infection in all patients with a clinical picture that fulfilled the adopted case definition of influenza-like illness: sudden onset of

fever (temperature ≥ 38,0 ºC), or history of fever in the last few days, and at least two of the following symptoms: cough, headache, sore throat, myalgia/arthralgia, rhinorrhea, vomiting, diarrhea and/or severe acute respiratory disease (including pneumonia) suggesting an infectious etiology. Also, the existence of an epidemiologic link defined as a stay or residence in an area where there was registry of transmission in the community of pandemic (H1N1) 2009 virus infection, during the seven days prior to the beginning of symptoms [4], was recorded.

Laboratory diagnosis of pandemic (H1N1) 2009 virus infection was performed by a real-time reverse-transcriptase polymerase-chain-reaction (RT-PCR) assay in agreement with the protocol established by the WHO [5].

We analyzed all the paper case report forms used for standardized data collection of the clinical manifestations of all patients with influenza-like illnesses who presented for medical observation in the various ambulatory care points in the central region of Portugal. All patients had samples submitted for laboratory diagnosis of pandemic (H1N1) 2009 infection during the first pandemic wave that started on 16 June 2009 (diagnosis of the first laboratory-confirmed infection) and ended on 28 August 2009, with an abrupt drop in new infections.

Statistical analysis

Variables were summarized as means and standard deviation or as median and interquartile range. For categorical variables, the percentages of patients in each category were calculated. The clinical features were compared between subgroups of patients infected versus non-infected with the pandemic (H1N1) 2009 virus using the Student's t-test, Chi-square test, or Fisher's exact test, as indicated. A multiple logistic-regression model was used considering the significant variables ($p < 0.1$) on the bivariate analysis to identify independent predictive factors associated with pandemic (H1N1) 2009 virus infection. Results are reported as odds ratios (OR) and 95% confidence intervals (95% CI).

For the multivariate analysis, the p value of the model, validity index, and area under the curve (AUC) of the receiver operating characteristic (ROC) model was calculated.

A two-sided p value of less than 0.05 was considered to indicate statistical significance. All statistical analysis was performed with the use of SPSS software (Statistical Package for Social Sciences, release 16. SPSS Inc., Chicago IL, USA).

Results

Samples from 828 patients with influenza-like illness were consecutively collected and submitted for diagnosis of pandemic (H1N1) 2009 virus, by RT-PCR. Infection with pandemic (H1N1) virus was confirmed in 255 (30.8%) cases.

Demographic data

The overall median age of the patients was 23 years (IQR, 13-35 years; range, 21 days to 88 years). Infected patients with pandemic (H1N1) 2009 virus infection had a lower median age [21 years (IQR, 16-27; range, 1 month to 84 years)].

Males (56%; 316 cases) were predominant. The distribution by age categories and pandemic (H1N1) 2009 virus infection showed a significant association ($p = 0.001$). Individuals from 20 to 29 years of age included 42.7% (109 cases) of the pandemic (H1N1) 2009 virus infected patients.

The proportion of non-infected to pandemic (H1N1) 2009 virus infected patients was greater in all the categories except ages 10 to 19 years and 20 to 29 years, with both representing 66.6% (170 cases) of all confirmed cases.

A small proportion of patients (11%; 28 cases) with pandemic (H1N1) 2009 virus infection were over 40 years old and only 12.2% (31 cases) were less than 10. Children under two years old represented 2.7% (7 cases) of the total number of patients with confirmed infection.

Clinical manifestations

Overall, 86% of the patients had fever (Table 1), which was more common (91%) in patients with confirmed pandemic (H1N1) 2009 virus infection than in negative patients (84%), ($p = 0.009$). Fever appeared simultaneously with other symptoms in 66% of the cases. In 31% of these cases fever appeared after other manifestations, both in patients with a positive test and also in cases negative for pandemic (H1N1) 2009 virus ($p = 0.854$). Fever was the first manifestation in only 3% of cases.

Other commonly reported signs and symptoms included myalgia (67%), cough (61%), headache (59%), sore throat (52%), rhinorrhea (32%), vomiting (16.6%) and diarrhoea (21%).

Bivariate analysis showed that pandemic (H1N1) 2009 virus infected patients were more likely to have

Table 1. Distribution of the symptoms of influenza-like illness

	Total (n = 828)		(H1N1) 2009				
			Non-confirmed H1N1 (n = 573)		Confirmed (n = 255)		p value
	n	(%)	n	(%)	n	(%)	
Cough	504	60.9%	296	51.7%	208	81.6%	<0.001 (*)
Headache	488	59.0%	324	56.6%	164	64.3%	0.038 (*)
Sore throat	431	52.1%	294	51.4%	137	53.7%	0.536 (*)
Rhinorrhea	263	31.8%	168	29.4%	95	37.3%	0.025 (*)
Dyspnea	56	6.8%	46	8.0%	10	3.9%	0.029 (*)
Epistaxis	12	1.5%	5	0.9%	7	2.7%	0.055 (**)
Sneezing	117	14.1%	66	11.5%	51	20.0%	0.001 (*)
Fever	710	85.9%	479	83.7%	231	90.6%	0.009 (*)
Myalgia	552	66.7%	370	64.7%	182	71.4%	0.059 (*)
Arthralgia	176	21.3%	114	19.9%	62	24.3%	0.155 (*)
Vomiting	137	16.6%	109	19.1%	28	11.0%	0.004 (*)
Diarrhoea	173	20.9%	133	23.3%	40	15.7%	0.014 (*)
Nausea	94	11.4%	73	12.8%	21	8.2%	0.058 (*)
Conjunctivitis	34	4.1%	22	3.8%	12	4.7%	0.565 (*)

(*) Chi-square test (**) Fisher's exact test

fever (90.6% versus 83.7%; p = 0.009), cough (81.6% versus 51.7%; p = 0.000), headache (64.3% versus 56.6%; p = 0.038), rhinorrhea (37.3%, versus 29.4%; p = 0.025), and sneezing (20.0% versus 11.5%; p = 0.000). However, they were less likely to have dyspnea, vomiting and diarrhoea than patients with a negative result for pandemic (H1N1) 2009 virus. Also, patients with pandemic (H1N1) 2009 virus infection had a greater median number of symptoms (5 symptoms versus 4, p = 0.000).

The assessment of the severity of the clinical case was made by the attending physician in the first appointment and the majority (80%) of cases was considered of low severity. During the period considered in our study, no patients had pneumonia or were admitted to an intensive care unit.

Factors associated with pandemic (H1N1) 2009 virus infection

A multiple logistic regression analysis model was used to study the covariates with significant association (p < 0.1) in the bivariate analysis: age, cough, headache, rhinorrhea, dyspnea, epistaxis, sneezing, fever, myalgia, vomiting, diarrhea, nausea, number of symptoms and epidemiologic link.

The non-significant variables (rhinorrhea, sneezing, diarrhea, nausea, number of symptoms and epidemiologic link) were removed to obtain an optimized model (greatest p value considered for backward regression) (Table 2). This model showed that the probability of having laboratory-confirmed pandemic (H1N1) 2009 virus infection decreased with age (OR, 0.982; 95% CI, 0.971 to 0.993; p = 0.001); was higher in patients with cough (OR, 4.450; 95% CI, 3.082 to 6.425; p = 0.000), epistaxis (OR, 3.855; 95% CI, 1.034 to 14.372; p = 0.044), fever (OR, 1.840; 95% CI, 1.106 to 3.060; p = 0.019), headache (OR, 1.451; 95% CI, 1.024 to 2.057; p = 0.036), and myalgia (OR, 1.491; 95% CI, 1.014 to 2.194; p = 0.042); and was lower in patients with dyspnea (OR, 0.418; 95% CI, 0.198 to 0.881; p = 0.022) and vomiting (OR, 0.463; 95% CI, 0.288 to 0.744; p = 0.001).

The p value and the area under the curve of the receiver operating characteristic (ROC) proved the model to be adequate to explain the presence of

Table 2. Analysis of factors associated with pandemic influenza A (H1N1) infection by multiple logistic regression

	Multiple logistic regression			Multiple logistic regression: optimized model		
Dependent variables	**OR**	**p value**	**95% CI for OR**	**OR**	**p value**	**95% CI for OR**
Age	0.983	0.002	[0.972; 0.994]	0.982	0.001	[0.971; 0.993]
Cough	4.177	<0.001	[2.684; 6.500]	4.450	<0.001	[3.082; 6.425]
Headache	1.482	0.097	[0931; 2.360]	1.451	0.036	[1.024; 2.057]
Dyspnea	0.421	0.031	[0.192; 0.926]	0.418	0.022	[0.198; 0.881]
Epistaxis	4.062	0.043	[1.046; 15.777]	3.855	0.044	[1.034; 14.372]
Fever	1.693	0.070	[0.958; 2.992]	1.840	0.019	[1.106; 3.060]
Myalgia	1.525	0.103	[0.918; 2.536]	1.491	0.042	[1.014; 2.194]
Vomiting	0.514	0.014	[0.302; 0.875]	0.463	0.001	[0.288; 0.744]
Diarrhoea	0.706	0.151	[0.439; 1.135]	-	-	-
Nausea	0.845	0.602	[0.450; 1.588]	-	-	-
Number of symptoms	1.005	0.9661	[0.791; 1.276]	-	-	-
p value (model)		< 0.001			< 0.001	
Area under ROC		0.734			0.726	
Overall Percentage		71.0%			71.7%	

OR: Odds Ratio 95% CI: 95% Confidence Interval

laboratory-confirmed pandemic (H1N1) 2009 virus infection.

The strength of association between symptoms and pandemic (H1N1) 2009 infection was not equally distributed (see odds ratios described above and in Table 2). The presence of cough (OR, 4.450), epistaxis (OR, 3.855), fever (OR, 1.840), headache (OR, 1.451), and myalgia (OR, 1.491) were strongly associated with the probability of having pandemic (H1N1) 2009 virus infection. The presence of dyspnea (OR, 0.418) and the presence of vomiting (OR, 0.463) were negatively associated with the probability of pandemic (H1N1) 2009 infection.

Thus, in the ambulatory setting, an increased probability of pandemic (H1N1) 2009 infection would be expected with 95% confidence, when associated with the presence of cough (3.082 to 6.425 times), epistaxis (1.034 to 14.372 times), fever (1.106 to 3.060 times), headache (1.024 to 2.057 times), and myalgia (1.014 to 2.194).

Discussion

We analyzed the clinical characteristics of the group of patients with pandemic (H1N1) 2009 virus infection diagnosed between June and August, 2009, in the central region of Portugal. During the first wave of the pandemic, the positivity rate for pandemic (H1N1) 2009 virus infection represented 31% of the group of patients presenting with influenza-like illnesses in the ambulatory setting but this infection rate was higher than in other regions of the European Community [6].

However, the incidence rate of influenza-like illness with a negative result for pandemic (H1N1) 2009 infection was very high (69%). This occurrence could be related to the circulation of other respiratory viruses in the community and to the strict isolation procedures implemented at that phase of the pandemic.

Vaccines against pandemic influenza were not widely available during its first wave and oseltamivir therapy and prophylaxis were used extensively as a strategy against pandemic influenza. Antivirals reduce the ability of the virus to replicate and do not provide immunity to the host but can form a critical component for the containment of the pandemic. It has been shown that they may aid in the prevention of infection, but may also reduce the level of its transmission and the severity of the associated disease [6]. It is unknown, however, how effective these interventions were in decreasing the infection rates. School closure for the summer term may have had an impact on the spread of disease, but on the other hand, summer vacation and travel activities could have had an important role in the dissemination of the infection.

In the central region of Portugal, young adults were the most affected by the pandemic (H1N1) 2009 infection, with a median age of 21 years. The distribution of the infection by categories according to age showed that 89% of the patients were less than 29 years old. Specific incidence rates for pandemic (H1N1) 2009 infection were greater in the age categories of 10 to 19 years (25.5%) and 20 to 29 years (35%); the distribution by age categories

observed in our region was similar to those reported in other countries and regions [7,8,9].

For the patients with pandemic (H1N1) 2009 virus infection, fever (91%) was the most common manifestation, being followed by cough (81.6%), myalgia (71.4%), headache (64.3%) and sore throat (53.7%). These manifestations appeared in similar proportions to those described in other European countries and the Unites States of America [9, 10, 11]. Manifestations such as diarrhoea and apyrexia were described in a greater proportion of patients from Asian countries. However, similar but not equal case definitions for influenza-like illness were used and the values admitted for fever were different, making comparisons a difficult task [8].

According to the data found in our study, influenza-like illness with pandemic (H1N1) 2009 virus infection was associated with a greater number of symptoms (5 symptoms versus 4, $p = 0.000$). Also, some of the symptoms were predictors of a greater probability of infection. The strength of association between symptoms and pandemic (H1N1) 2009 infection was not equally distributed. Some of the symptoms were positively correlated with the probability of having pandemic (H1N1) 2009 virus infection, namely cough, epistaxis, fever, headache, and myalgia. In our study, lack of dyspnea or vomiting predicted a greater probability of having pandemic (H1N1) 2009 infection compared to the patients who had dyspnea or vomiting; we have to stress that all the cases included in our study presented as mild febrile illnesses without complications and that other viruses were also circulating at the time.

Our results may contribute to a more accurate case definition of influenza-like illness in future influenza pandemics in which a different weight or score should be attributed to different symptoms to predict those patients most likely to be infected. However, the accuracy may depend on the proportion of other infections associated with influenza-like illnesses circulating in the community. As was expected, the sensitivity of the case definition for influenza-like illness used rose during the winter months when most cases of influenza-like illnesses were associated with pandemic (H1N1) 2009 virus infection (data not shown).

The severity of the disease during the first wave of pandemic (H1N1) 2009 virus infection observed in our region was low, similar to that described in other countries [12]. There were no cases of pneumonia, respiratory failure requiring ventilator support, or deaths during the first wave of pandemic (H1N1) 2009 virus infection.

To conclude, in the central region of Portugal, the first wave of pandemic (H1N1) 2009 virus infection was associated with cases of low severity occurring most often in patients younger than 29 years. Also, the incidence rate for pandemic influenza was lower than that of other common febrile illnesses regularly observed during summer months. Probably, early diagnosis, use of oseltamivir and strict isolation procedures implemented at the time could explain the lower proportion of confirmed pandemic (H1N1) 2009 virus infections in the context of the case definition used for influenza-like illness.

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