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Clinical differences between influenza A (H1N1) virus and respiratory infection between the two waves in 2009 and 2010

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Background: The purpose of the present retrospective study was to examine the clinical differences between patients hospitalized with H1N1 virus and those hospitalized with nonvirus respiratory tract infection in 2009 and 2010.

Methods: Adult patient data were collected from three tertiary hospital centers. Real-time reverse transcriptase polymerase chain reaction testing was used to confirm the diagnosis. We included 106 H1N1-positive patients (52 from 2009 and 54 from 2010). These data were compared with those from 108 patients with H1N1-negative respiratory tract infection (51 patients from 2009 and 57 from 2010).

Results: In 2009, the mean age was 36.4 years for H1N1-positive patients versus 46.4 years for H1N1-negative patients, and mean body mass index (BMI) was 26.4 kg/m^2 patients and 28.1 kg/m^2, respectively. In 2009, seven patients required intubation, six of whom were H1N1-positive. In 2010, the mean age was 43.8 years for H1N1-positive patients versus 60.2 years for H1N1-negative patients, and mean BMI was 32.3 kg/m^2 and 26.9 kg/m^2, respectively. In 2010, six patients required intubation, three of whom were H1N1-positive. Abnormal chest x-ray findings were found significantly more frequently in H1N1-negative patients than in H1N1-positive patients.

Conclusion: In comparison with 2009, H1N1-positive patients in 2010 were older, were more likely to be obese, and had more severe clinical and laboratory perturbations. However, this did not affect their outcomes. H1N1-negative patients were older in comparison with those who were H1N1-positive, and had more severe clinical and laboratory perturbations.

Keywords: clinical characteristics, influenza A, H1N1, respiratory infection

Introduction

In June 2009, the World Health Organization (WHO) prepared the medical community for a novel H1N1 influenza pandemic.[1–4] During this pandemic, an increasing number of countries reported confirmed H1N1-positive cases in 2009, and approximately 2900 deaths were reported in Europe.[4] Even though H1N1-positive patients in many tertiary centers were accurately diagnosed and promptly treated, numerous pathogens were incorrectly diagnosed as H1N1-positive in one report.[5] From a health systems point of view, this misdiagnosis of H1N1/2009 may have led to underestimation of other serious conditions.[5] For the same reason, a large number of patients may have been unnecessarily treated with oseltamivir, resulting in unnecessary cost and exposure to the side effects of this agent, as well as excessive implementation of infection control procedures in hospitals.[6–9]

Clinically, influenza infection is held responsible for excess mortality, especially in elderly patients and those with comorbidities.[10] It may lead to community-acquired

pneumonia, the incidence and mortality from which is difficult to ascertain, given the year-to-year variability in influenza activity and, at least in some studies, a potential selection bias. Thus, remarkable variance in prevalence of this condition has hitherto been reported.[11–13] Little is known about severe community-acquired pneumonia requiring intensive care unit admission, but influenza-associated community-acquired pneumonia appears to have been infrequent.[14,15]

Importantly, a second wave of influenza was reported in 2009,[16,17] followed by others in 2010.[18,19] Mutations to the virus had already been observed in 2009[20–23] and several others continued in the following influenza seasons.[18,24] More ominously, resistance to oseltamivir ensued from the first wave and reached a peak in the 2010 pandemic, raising concerns about the possibility of treatment failure.[21,25–28]

However, to the very best of our knowledge, differences in H1N1 infections between 2009 and 2010 have not been adequately investigated. The present study examined potential clinical differences between the 2009 and 2010 waves of H1N1 infection, as well as differences between H1N1-positive and H1N1-negative patients.

Materials and methods

Subjects

Over two seasons, (August 10, 2009 to December 25, 2009 and January 31, 2010 to September 10, 2010), 133 adult patients with H1N1-positive influenza were hospitalized in three major tertiary centers in Greece. Of these, 27 were excluded from this study due to incomplete data, and 106 H1N1-positive patients were included (52 from 2009 and 54 from 2010). Their data were compared with those for 108 patients with lower respiratory tract infection (pneumonia) of other etiology (52 from 2009 and 54 from 2010). In the 2009 wave, 17 of those with documented H1N1 were female and 35 were male; in 2010, 26 were female and 28 were male. One woman was pregnant, in month 8 of her pregnancy at diagnosis, and was discharged without any complications. H1N1-positive patients were admitted with influenza-like symptoms (sore throat, cough, rhinorrhea, nasal congestion) and fever > 37.5°C, as defined by the Centers for Disease Control and Prevention, WHO, and initial studies.[1–4,29] In all cases, antiviral treatment was initiated immediately and discontinued depending on the results. One H1N1-negative patient died in 2009, and three in 2010. Six H1N1-positive patients died in 2009, and three in 2010. In total, seven patients died in 2009 and six in 2010. This retrospective data collection was approved by the investigational review boards of the three tertiary hospitals involved.

Procedure

Pharyngeal or nasopharyngeal swabs were taken upon admission, according to the protocol from the US Centers for Disease Control, as recommended by WHO. Swabs were tested using real-time reverse transcriptase polymerase chain reaction (RT-PCR) and the average time between obtaining the samples and testing was 8–48 hours.[2] In the event of negative results for H1N1, antiviral treatment was stopped. None of the H1N1-positive patients had received antiviral treatment before hospital admission. Patients were assessed by CURB-65 severity score for community-acquired pneumonia upon admission[30] (Table 1). In addition, epidemiologic data, laboratory results, chest x-rays, and clinical outcomes were recorded. We included only patients with full data to enable meaningful correlation.

Statistical analysis

Data are presented as the mean ± standard deviation for continuous variables. The unpaired *t*-test was used to compare normally distributed variables. The unpaired Student's *t*-test was used to detect differences between H1N1-positive and H1N1-negative patients. For categorical variables, the percentages of patients in each category were calculated and compared by Chi-square and Kruskal–Wallis test. A $P < 0.05$ was considered to denote statistical significance.

Results

The main differences between 2009 and 2010 for H1N1-infected patients were seen in age ($P < 0.009$), body mass index (BMI, $P < 0.01$), temperature ($P < 0.004$), headache ($P < 0.025$), fatigue ($P < 0.018$), C-reactive protein upon discharge ($P < 0.004$), days with fever before admission ($P < 0.005$), oxygen saturation upon admission ($P < 0.035$), creatinine upon admission ($P < 0.034$), alanine transaminase upon admission ($P < 0.001$) and discharge ($P < 0.001$), white blood cell count upon discharge ($P < 0.008$), partial oxygen saturation upon admission ($P < 0.001$), days on oseltamivir treatment ($P < 0.01$), and number of patients with underlying disease ($P < 0.035$). Obesity was more frequent in 2010 (35 patients, 64.8%). According to the WHO global BMI database, a patient is considered obese when BMI is ≥30. Table 1 summarizes the clinical and laboratory characteristics, as well as outcomes for all patients.

Risk factors

The mean age of patients hospitalized with H1N1 was lower (40.2 years versus 53.8 years, $P < 0.01$) than that of those hospitalized with pneumonia of other etiology, and

Table 1 Patient characteristics

	August 10, 2009–December 25, 2009					January 31, 2010–September 10, 2010					95% CI HINI (–) HINI (+)
	HINI (+) n = 52 mean		HINI (–) n = 51 mean		SD	HINI (+) n = 54 mean		HINI (–) n = 57 mean		SD	
Risk factors											
Age	36.4		46.4		16/20.6	43.8		60.2		18/18.5	–21,532 to –6,423 –14,009 to –810
Gender	17f/35m		24f/27m			26f/28m		24f/33m			–299 to 155
BMI (kg/m^2)	26.4		28.1		4.2/4.6	32.3		26.9		6.4/4.5	–611 to 2,957 –8,000 to –3,782
Smoking	19 (36.5%)		33 (64.7%)			24 (44.4%)		31 (54.3%)			
Vaccination	3 (5.7%)		1 (1.9%)			1 (1.8%)		1 (1.7%)			
Asthma	14 (26.9%)		11 (21.5%)			7 (12.9%)		13 (22.8%)			
COPD	12 (23%)		16 (31.3%)			15 (27.7%)		13 (22.8%)			
IPF	1 (1.9%)		0 (0%)			1 (1.8%)		0 (0%)			
CHD	6 (11.5%)		10 (19.6%)			9 (16.6%)		11 (19.2%)			
DM	12 (23%)		10 (19.6%)			12 (22.2%)		13 (22.8%)			
Cancer	8 (15.3%)		7 (13.7%)			6 (11.1%)		8 (14%)			
Clinical findings											
Fever	37.9		37.86		0.7/0.9	38.06		38.04		0.9/0.7	
Cough	48 (92.3%)		47 (92.1%)			50 (92.5%)		53 (92.9%)			
Sputum	34 (65.3%)		41 (80.3%)			39 (72.2%)		36 (63.1%)			
Fatigue	29 (55.7%)		28 (54.9%)			24 (44.4%)		38 (66.6%)			
Myalgia	28 (53.8%)		30 (58.8%)			28 (51.8%)		29 (50.8%)			
Headache	17 (32.6%)		10 (19.6%)			12 (22.2%)		24 (42.1%)			
Hemoptysis	11 (21.2%)		14 (27.4%)			14 (25.9%)		13 (22.8%)			
Vomiting	6 (11.5%)		8 (15.6%)			4 (7.4%)		9 (15.7%)			
Nausea	6 (11.5%)		8 (15.6%)			4 (7.4%)		9 (15.7%)			
Rash	2 (3.8%)		2 (3.9%)			2 (3.7%)		0 (0%)			
Laboratory findings (upon admission)											
WBC (×10^3/μL)	7632.3	17,250	10,227.1	3760.7/5049.4	20,000	8362.9	70,300	10,334	9667.8/5044	24550	
PCT (ng/mL)	2.3	17	2.7	2.4/1.5	7.9	4.175	25	2	0.5/0.2	10.9	
CRP (mg/dL)	4.9	17	8.8	4/10.1	44	4.47	19	6.3	4.1/7.4	39	
Urea (mg/dL)	29.4	92	32.7	14.5/14.8	60	34.3	255	38.1	35.5/15.7	71	
Creatinine (mg/dL)	0.9	1	0.9	0.2/0.2	1	0.8	1	0.9	0.1/0.2	1	
AST (IU/L)	45.8	277	36	52.7/26.8	150	35.8	157	29.9	27.9/13.8	54	
ALT (IU/L)	42.4	155	33.1	37.7/22	110	42.5	154	26.6	31.9/13	57	
Abnormal chest x-ray	11 (21.1%)		20 (39.2%)			17 (31.4%)		26 (45.6%)			
pO_2 (mmHg)	73.3	61	69	13.5/12.2	56	69.4	75	60.5	15.5/10.2	46	
Outcome											
Days of hospitalization	5.5	16	5.6	2.6/3.1	18	6.6	20	6.8	3.6/3.8	20	
Days with fever	2.3	5	3.3	0.9/2.3	15	2.6	15	4.5	2.5/3.6	20	
Days under oseltamivir	5.6	14	0.9	2.2/1.3	5	4.9	13	0	2.3/0	0	

(*Continued*)

Table 1 (*Continued*)

	August 10, 2009–December 25, 2009			January 31, 2010–September 10, 2010			95% CI H1N1 (–)
	H1N1 (+) n = 52 mean	H1N1 (–) n = 51 mean	SD	H1N1 (+) n = 54 mean	H1N1 (–) n = 57 mean	SD	H1N1 (+)
ICU admission	6 (11.5%)	1 (1.95)		3 (5.5%)	3 (5.2%)		
CURB-65 class							
II	18 (34.6%)	13 (25.4%)		21 (38.8%)	20 (35.8%)		
III	25 (48)	24 (47)		22 (40.7%)	25 (43.8%)		
IV	9 (17.3%)	14 (27.4%)		11 (20.3%)	12 (21%)		

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; IPF, interstitial pulmonary fibrosis; CHD, coronary heart disease; DM, diabetes mellitus; WBC, white blood count; PCT, procalcitonin; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ICU, intensive care unit; f, female; m, male; CI, confidence interval.

H1N1-positive infection occurred in people with higher BMI (29.4 kg/m^2 versus 27.5 kg/m^2, $P < 0.01$, Table 2). Nevertheless, the age distribution was similar between H1N1-positive and H1N1-negative pneumonias in 2010, and there was no difference in BMI between H1N1-positive and H1N1-negative cases in 2009 (Table 3). Pneumonia was defined as lower respiratory tract infection based on laboratory and radiologic evidence. There was no difference in susceptibility between men and women. There was no difference in other risk factors (smoking, underlying chronic respiratory disease, severe comorbidities) between patients with H1N1-positive and H1N1-negative pneumonia (Table 1).

Clinical findings

Patients with H1N1-positive pneumonia had fewer days with fever before admission (3.19 versus 4.13 days, $P < 0.04$), but presented with higher temperatures (38.83°C versus 38.50°C, $P < 0.01$, Table 2). However, these clinical parameters differed only in the 2009 population. In 2010, significant differences were observed in frequency of reported symptoms of headache and fatigue, which were higher in patients with pneumonia of other than H1N1 etiology ($P < 0.025$ and $P < 0.018$ for headache and fatigue, respectively, Table 3). CURB-65 results were Class II–IV and no significant differences were observed.

Laboratory findings

On average, patients with H1N1-positive pneumonia had a better laboratory profile, with lower white blood cell count on admission (8004 × 10^3/μL versus 10,284.6 × 10^3/μL, $P < 0.01$), and lower C-reactive protein levels on admission (4.6 mg/dL versus 7.4 mg/dL, $P < 0.01$) and on discharge (1.4 mg/dL versus 3 mg/dL, $P < 0.01$), fewer findings on first chest x-ray ($P < 0.02$), and better oxygen saturation upon admission (93.7 mmHg versus 92.4 mmHg, $P < 0.01$, Table 2). An unexplained finding was the high aspartate transaminase values on admission and on discharge seen in 2010 H1N1-positive pneumonia cases in comparison with other cases of pneumonias in the same year (Table 3). Procalcitonin levels were 2.6 ng/mL for H1N1-positive patients and 2.7 ng/mL for H1N1-negative patients. Regarding antigens and antibodies, the results were positive for *Streptococcus pneumonia* in urine samples in five H1N1-positive patients and no antibody results were positive. Among the H1N1-negative patients, six results were positive for *S. pneumonia* in urine samples, again without any positive antibodies.

Table 2 Significant differences between H1N1 (+) and H1N1 (–) pneumonias in 2009 and 2010

	Unpaired t-test	H1N1 (+) mean values	H1N1 (–) mean values	95% CI H1N1 (–) H1N1 (+)
Risk factors				
Age (years)	$P < 0.01$	40.2	53.8	–21,532 to –6423 –14009 to –810
BMI (kg/m^2)	$P < 0.01$	29.4	27.5	–611 to 2957–8000 to –3782
Clinical findings				
Days with fever ≥ 38°C before admission	$P < 0.04$	3.1	4.1	–2411 to –024 –2728 to 024
Fever temperature upon admission	$P < 0.01$	38.8	38.5	–5334 to 2321 –1047 to –445
Headache	$P < 0.03$	0.217 (32.6%)/ 12 (22.2%)	0.410 (19.6%)/ 24 (42.1%)	
Laboratory findings				
WBC upon admission (×10^3/μL)	$P < 0.01$	8004.0	10,284.62	–2,054,882 to 1,841,098 –3,577,736 to 2,114,502
CRP upon admission (mg/dL)	$P < 0.01$	4.6	7.4	–1030 to 5976 –1142 to 2024
CRP upon discharge (mg/dL)	$P < 0.01$	1.4	3	278 to 3467 –056 to 999
Patients with abnormal chest x-ray	$P < 0.02$	26%	42%	
SpO_2 on admission (mmHg)	$P < 0.01$	93.7	92.4	
Outcomes				
Days under oseltamivir	$P < 0.01$	5.3	0.4	635 to 1,325 –201 to 1,584

Abbreviations: BMI, body mass index; CI, confidence interval; WBC, white blood cells; CRP, C-reactive protein; SpO_2, oxygen arterial partial pressure.

Outcomes

The clinical presentation of H1N1-positive pneumonias was mainly mild; only six patients required admission and intubation in intensive care and mechanical ventilation in 2009 and three patients required this treatment in 2010. Nevertheless, the course of H1N1-positive pandemic pneumonias seemed to be more aggressive in 2009 compared with pneumonias of other etiology in 2010, because the number of patients with H1N1-positive pneumonia who needed mechanical support was higher overall than the number of patients with other types of pneumonia. In 2009, six of seven patients who were intubated were H1N1-positive, as compared with three of six who were intubated in 2010 (Table 1).

Discussion

Major advances in influenza surveillance and prompt diagnosis by real-time RT-PCR have been accomplished worldwide in recent years.[1,20,31] According to the Greek National Surveillance Center, influenza A (H1N1) 2009 virus predominated in Greece in 2009/2010 and 2010/2011, with a total increase of laboratory-confirmed virus-positive cases, despite the higher percentage of vaccinated subjects.[29] Experience with previous pandemics has demonstrated that the second season of transmission may, in some cases, be worse than the initial one.[16,17]

In our report, important differences were identified between 2009 and 2010 for H1N1 infection. These pertained to epidemiologic characteristics (age, BMI), clinical presentation (temperature, headache, fatigue, days with fever before admission, oxygen saturation upon admission) and laboratory values (C-reactive protein upon discharge, creatinine upon admission, alanine transaminase upon admission and discharge, white blood cell count upon discharge), days on oseltamivir treatment, and number of patients with underlying disease. In comparison with 2009, H1N1-positive patients in 2010 were overall older, more likely to be obese, and had more severe clinical and laboratory perturbations, but this did not affect the outcomes. These findings suggest that the virus has possibly undergone a mutation, leading to a different presentation.[32–35] The prolonged time on oseltamivir raises concern about the potential for development of resistance to this agent.[33] Several studies testify to H1N1 mutations and, at the same time, resistance to antiviral treatment has been observed during both waves worldwide.[18,20–28] In Greece, several studies have provided data on H1N1 mutation, which is possibly associated with disease severity and antiviral resistance.[32–36]

The main differences between H1N1-positive and H1N1-negative patients were age, BMI, underlying respiratory distress, creatinine and urea upon discharge, partial oxygenation, days with high fever, and chest x-ray findings. Overall, H1N1-negative patients were older and had more severe clinical and laboratory perturbations. In addition, it was observed that although directions and information

Table 3 Significant differences between H1N1 (+) or H1N1 (–) pneumonias in 2009 and 2010

		August 10, 2009–December 25, 2009			January 31, 2010–September 10, 2010		CI 95% H1N1 (–) H1N1 (+)
		Mean values			Mean values		
		H1N1 (+)	H1N1 (–)		H1N1 (+)	H1N1 (–)	
Risk factors							
Age (years)	$P < 0.09$	36.4	46.2	NS	43.8	60.2	–21,532 to –6423 –14,009 to –810
BMI (kg/m^2)	NS	26.4	28.1	$P < 0.01$	32.3	26.9	–611 to 2957 –8000 to –3782
Clinical findings							
Fever ≥ 38°C before admission	$P < 0.04$	38.9	38.4	NS	38.7	38.5	–5334 to 2321 –2728 to 024
Days with fever ≥ 38°C before admission	$P < 0.005$	2.5	3.9	NS	2.6	4.5	–2411 to –024 –1047 to 445
Headache	NS	0.317 (32.6%)	0.410 (19.6%)	$P < 0.025$	0.212 (22.2%)	0.424 (42.1%)	
Fatigue	NS	0.529 (55.7%)	0.528 (54.9%)	$P < 0.018$	0.424 (44.4%)	0.638 (66.6%)	
Laboratory findings							
pO_2 upon admission (mmHg)	NS	73.3	69	$P < 0.001$	69.4	60.5	4265 to 12,905 –1730 to 9540
Creatinine upon admission (mg/dL)	NS	0.9	0.9	$P < 0.25$	0.8	0.9	–105 to 075 –006 to 159
AST upon admission (IU/L)	NS	45.8	36	$P < 0.001$	42.5	26.6	–2043 to 14,079 –6189 to 26,178
WBC upon discharge ($\times 10^3/\mu L$)	NS	7491.7	7788.4	$P < 0.008$	6642.5	7999.8	–1,272,059 to 849,267 –1,707,706 to 3,405,983
ALT upon discharge (IU/L)	NS	40.5	41.1	$P < 0.001$	43	25.3	–1087 to 32,555 –15,373 to 10,379
CRP upon discharge (mg/dL)	$P < 0.004$	1.6	4.1	NS	1.1	2.2	278 to 3467 –056 to 999
Outcomes							
Days under oseltamivir	$P < 0.01$	5.6	0.9	$P < 0.01$	4.9	0	635 to 1325–201 to 1584
Days with fever while hospitalized	NS	2.3	3.3	$P < 0.002$	2.6	4.5	

Abbreviations: BMI, body mass index; CI, confidence interval; pO_2, arterial oxygen partial pressure; WBC, white blood count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein; NS, not statistically significant.

were distributed to the general public, a large number of people were not vaccinated, leaving them vulnerable to the virus.[36–38]

This study had several limitations. The most important are its small number of participating hospitals and retrospective design. Moreover, we did not examine our samples for H1N1 mutation, nor did we ascertain resistance to antiviral agents. Nevertheless, these assumptions are realistic, based on studies that have already demonstrated H1N1 mutations and strains with antiviral resistance. Another limitation was the difficulty in defining the etiology of other pneumonias and lack of availability of respiratory samples, which has been a frequent problem in the relevant studies.[39,40] A further limitation was the time interval between specimen acquisition and diagnosis of H1N1, some patients received unnecessary treatment with oseltamivir, which in turn induced adverse effects such as nausea and vomiting. Nonetheless, these cases were few and did not affect the clinical outcome.

A further question to be answered in terms of prompt treatment is whether addition of a macrolide antibiotic can suppress virus-induced cytokine production. Indeed, these agents are well known for their immunomodulatory and anti-inflammatory properties.[41,42] It has already been shown that macrolides may be efficacious in viral infections, although the dose and/or type of macrolide, as well as route

of administration, need additional elucidation.[42–44] Similarly, N-acetylcysteine, which is widely used to clear mucus from the airways and has protective potential in the respiratory tract,[45,46] might be a useful therapeutic adjunct. Arguably, such agents merit careful consideration in H1N1 infection, based on previously published results.[42–46]

In comparison with other studies, the main difference seen was that the mean age of H1N1-positive patients in our study was substantially lower than that previously reported.[47–49] The total percentage of respiratory diseases and comorbidities, such as immunosuppressive disease (diabetes mellitus, cancer) and coronary heart disease, in our study was in line with prior reports.[47] However, another study reported that a frequency of these conditions that was 25% less than in our study.[48] Moreover, days of symptoms, oseltamivir treatment, and hospitalization in our report agree with prior publications.[47,48] Female H1N1-positive patients were more prevalent than males, as already shown.[47,48] Nevertheless, some have found that male H1N1-positive patients were more frequent than women.[49] Several factors, including white blood cell count, C-reactive protein levels, myalgia, fatigue, headache, and nausea, were slightly elevated in our study in comparison with others.[49] This may be due to immediate empiric administration of antiviral treatment pending swab results.

Finally, our dataset supports the idea that establishing collaboration between tertiary hospitals for collection of data pertaining to severe respiratory infections would give additional insight to assist in prevention and control of the annual influenza pandemic. One possible way to achieve this could be the availability of medical records from specialized centers via the Greek National Surveillance Centre. This would enable recording of the special characteristics of influenza A (H1N1) infections in order to generate pooled data and promote deeper understanding in this field.

Disclosure

The authors report no conflicts of interest in this work.

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