

ORIGINAL PAPER
ΕΡΕΥΝΗΤΙΚΗ ΕΡΓΑΣΙΑ

**Preliminary analysis of adult patients
with 2009 H1N1 influenza hospitalized
in a University Department in Athens,
May–August 2009**

OBJECTIVE In April 2009 the first cases of novel influenza A H1N1 were registered in Mexico, since when the disease spread rapidly worldwide, becoming a pandemic. This paper describes the clinical features and course of the disease in adults hospitalized with proven H1N1 infection in a reference center in Athens, and explores the risk factors for H1N1 pneumonia. **METHOD** Retrospective medical chart reviews were made to collect data on the hospitalized patients. H1N1 infection was confirmed in specimens with the use of a real-time reverse transcriptase-polymerase chain reaction assay (RT-PCR). **RESULTS** From 15th May to 15th September 2009, 58 patients were hospitalized with H1N1 infection, of whom 52% presented with flu-like symptoms and had a benign course. Nearly 30% had one or more underlying medical conditions. A total of 28 of the 58 patients (48%) presented with pneumonia, and there were 7 intensive care admissions, but no deaths. Four patients developed acute respiratory distress syndrome (ARDS) and therefore required mechanical ventilation. The patients with pneumonia were older (36 vs 26, $p=0.003$), more hypoxemic (39% vs 7%, $p=0.01$) and presented higher serum levels of alanine aminotransferase (SGOT) (43.2 vs 25.5, $p=0.01$), creatine phosphokinase (CPK) (418 vs 127.5, $p=0.01$) and lactate dehydrogenase (LDH) (345 vs 171, $p=0.002$) than the other patients hospitalized with H1N1. **CONCLUSIONS** During the evaluation period (May–August 2009) it was observed that H1N1 influenza can cause pneumonia devoid of bacterial infection, with prognostic factors for its development being high serum levels of LDH at admission and the smoking habit.

The novel swine-origin influenza A (H1N1) virus was identified on April 15th 2009 as the definitive cause of large numbers of febrile respiratory illnesses in Mexico and the United States (US). Rapid spread of the virus throughout many countries around the world followed, forcing the World Health Organization (WHO) to declare a pandemic on June 11th, 2009. The 2009 H1N1 virus contained a unique combination of gene segments that had not been previously identified in humans or animals. As of 20th September 2009, human infection with 2009 H1N1 virus had been identified in 191 countries and territories and over 277,607 laboratory-confirmed cases of 2009 H1N1 influenza had been reported, with at least 3,205 deaths, according to the US Centers for Disease Control (CDC).

Preliminary comparison with seasonal influenza suggests

that pandemic 2009 influenza A (H1N1) disproportionately affects people in younger age groups and causes generally mild disease. Information regarding the clinical spectrum of illness and risk factors for severity among persons hospitalized for the treatment of 2009 H1N1 influenza is still emerging.¹

In Greece, an enhanced surveillance system for influenza A (H1N1) was set up on the 30th April 2009. The main target was travelers returning from affected areas and their close contacts. All probable cases of influenza A (H1N1) were managed in designated reference hospitals. On May 18th 2009 the first case of influenza A (H1N1) was detected in a 19 year-old male, who had returned to Greece from New York City two days earlier.²

This case series describes the epidemiological and clini-

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2011, 28(2):261–266

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Προκαταρκτική ανάλυση
νοσηλευόμενων ασθενών με γρίπη
H1N1 σε Πανεπιστημιακή Κλινική,
από το Μάιο–Αύγουστο 2009,
στην Αθήνα

Περίληψη στο τέλος του άρθρου

Key words

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cal characteristics of the first 58 patients with laboratory-confirmed influenza A (H1N1) infection hospitalized in the Special Infections Unit of the 1st Department of Respiratory Medicine, Medical School of Athens University, "Sotiria" Hospital, during May–August 2009, and compares two groups classified according to the presence or absence of pneumonia at hospital admission. "Sotiria" hospital was during that time period one of the four (4) reference hospitals for H1N1 infection in Athens.

The information presented in this study focuses on the disease characteristics at the early stage of the evolving pandemic in Greece.

MATERIAL AND METHOD

A retrospective study was made of patients hospitalized for at least 24 hours who presented with an influenza-like illness, confirmed as influenza A (H1N1) by real-time reverse transcriptase-polymerase chain reaction assay (RT-PCR) at the Pasteur Institute laboratories of Athens. The clinical features of the patients were retrieved from the medical records of the unit. Information was gathered regarding demographic data, preexisting medical conditions, clinical aspects of the disease and patient outcome. The hospital scientific committee and institutional review board for investigations approved the study.

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) v. 17 software. Data were presented as number (proportions) and mean \pm SD. Qualitative or categorical variables were compared with the Chi-square or Fisher's exact tests, and quantitative continuous variables were compared using the unpaired Student's t-test or the Mann-Whitney non-parametric test, as appropriate.

Multivariate analysis

Logistic regression analysis to predict pneumonia development was performed, using as independent variables those found significant in univariate analyses. P values for all statistical analyses were two-sided with $p < 0.05$ considered significant.

Definitions

Clinical stability: The time to resolution of abnormalities in vital signs, ability to eat, and restoration of mental status in patients with pneumonia.

Obesity: BMI 30–39.9 in adults 18 years or older.

Morbid obesity: BMI > 40 .

RESULTS

During the time period 15th May–30th August 2009,

126 patients presenting with influenza-like illness were hospitalized in the department and underwent RT-PCR testing, of whom 58 (46%) were H1N1 positive. Hospitalization was not representative of disease severity, because initially it was used as a mean of isolation. Seven patients with confirmed H1N1 (12%) were admitted to the ICU. No deaths were reported.

Of these patients, 16/58 (28%) were transferred from other health centers, 10 of the 16 from rural areas of Greece. Twenty H1N1 confirmed patients reported family and work contacts prior to infection and 16/58 (35%) reported a recent return from a trip to the Greek islands.

Table 1 shows the characteristics of the 58 study patients with confirmed H1N1 infection. The mean age of the patients was 30.8 ± 13 years, median 31 years, range 15–71 years, while 77% of the patients were younger than 35 years. No significant difference was identified between sexes, with 31/58 (53%) being males.

Clinical characteristics of the patients with H1N1

Symptoms at presentation as reported in table 1 included fever > 38 °C as a universal symptom (96%), cough (83%), headache (75%) and myalgias-arthralgias (70%). Diarrhea and or vomiting were reported by 27% of patients. Regarding past medical history 18/58 (31%) had an underlying medical condition, the most common of which were bronchial asthma (15%), chronic obstructive pulmonary disease (COPD) and arterial hypertension. The mean time from symptom onset to diagnosis of influenza A (H1N1) infection was 3.06 ± 2.4 days.

On admission, 20/58 patients (34%) had leucopenia, 25/58 (41%) had lymphopenia, 5/58 (9%) had thrombocytopenia, and 13/58 had hypoxemia ($\text{PaO}_2 < 60$ mmHg) (22%) (tab. 2).

Regarding radiological findings, 28/58 of the patients (48%) presented with lung opacity consistent with pneumonia; chest X-ray findings included an infiltrate limited to one lobe in 16 patients, and multilobar infiltrates in 12 patients, with the majority of them (9/12) bilateral in the lower lobes (tab. 2).

Characteristics of patients with pneumonia

The characteristics of the 28 patients with pneumonia in comparison with the other patients with H1N1 influenza are presented in table 3. The median age of the patients with pneumonia was 36 years (range 15–71 years) and 43% had an underlying medical condition. Patients with

Table 1. Characteristics of the patients with H1N1 infection.

Variable	n=58	%
Age (years)	30.8±13	
Age groups:		
15–25 years	25	43
25–35 years	16	28
>35 years	17	29
Gender; male/female	31/27	53.4/46.6
Co-morbidities		
Bronchial asthma	9	16
COPD	3	5
Arterial hypertension	3	5
Diabetes mellitus	2	3
Obesity*	2	3
Current smokers	18	33
Prior antibiotic treatment	18	31
Symptoms		
Days from onset	3.06±2.4	
Sudden onset of symptoms	12	22
Fever	55	96
Cough	48	83
Fatigue	43	76
Headache	43	75
Myalgia or arthralgia	40	70
Rhinorrhea	37	66
Shivering	33	58
Dyspnea	32	56
PaO ₂ <60 mmHg	13	22
Diarrhea and or vomiting	15	27

*Obesity: BMI >30 kg/m²; COPD: Chronic obstructive pulmonary disease; PaO₂: Partial pressure of arterial oxygen

pneumonia had worse oxygenation (p=0.01) at onset of pneumonia. The majority of them were smokers (54%), had received antibiotics prior to their admission to the hospital (46%) and presented at the emergency department later than the others (3.74 vs 2.34 days, p=0.02). Certain medical conditions, such diabetes mellitus, were not found associated with of H1N1 pneumonia in this series.

The symptoms presenting in a more pronounced form in pneumonia patients than in those with simple influenza illness were dyspnea (75% vs 37%, p=0.01) and shivering (37% vs 77%, p=0.005). Regarding laboratory findings pneumonia patients presented higher serum levels of lactate dehydrogenase (LDH) (345 vs 171, p<0.001), alanine aminotransferase (SGOT) (43.3 vs 25.5, p=0.01) and creatine

Table 2. Selected abnormalities detected in the patients with H1N1 infection*.

	n=58	%
Leucopenia (WBC <5,000/μL)	20	34
Leucocytosis (WBC >10,000/μL)	12	21
Lymphocyte count <1,000/μL	25	41
Elevated serum SGOT (>55 IU/L)	10	17
Elevated serum CPK (>240 IU/L)	15	31
Elevated serum LDH (>225 IU/L)	18	36
PaO ₂ <60 mmHg	13	22
PaO ₂ /FiO ₂ <250	6	10
Chest infiltrate	28	48
Unilateral	16	57
Bilateral	9	32
Multilobar	12	43

*Laboratory values are based on Custer and Raw

WBC: White blood cells; LDH: Lactate dehydrogenase; SGOT: Alanine aminotransferase; CPK: Creatine phosphokinase; PaO₂: Partial pressure of arterial oxygen; PaO₂/FiO₂: Ratio of PaO₂ to the fraction of inspired oxygen (FiO₂) were measured while the patients were breathing ambient air

Table 3. Characteristics of patients with confirmed H1N1 infection.

	H1N1 flu without pneumonia n=30	Pneumonia n=28	p
Gender, male/female	15/15	16/12	0.8
Age, years	26±10	36±15	0.003
Smokers	3 (12%)	15 (54%)	0.003
Co-morbidities	6 (20%)	12 (46%)	0.1
Days from illness onset to admission	2.34±2	3.7±2.5	0.02
Prior antibiotic treatment	5 (17%)	13 (46%)	0.04
Shivering	11 (37%)	22 (77%)	0.005
Dyspnea	11 (37%)	21 (75%)	0.01
PaO ₂ <60 mmHg	2 (7%)	11 (39%)	0.01
LDH, IU/L	171±80	345±250	0.002
SGOT, IU/L	25.5±14	43.2±32	0.01
CPK, IU/L	127.5±126	418±584	0.01
LOS, days	5.8±4.1	6.07±3.7	0.8
Stability day	3.3±2	2.7±1.2	0.23
ICU admission	1 (3%)	6 (21%)	0.048

LDH: Lactate dehydrogenase; SGOT: Alanine aminotransferase; CPK: Creatine phosphokinase; LOS: Length of hospital stay; PaO₂: Partial pressure of arterial oxygen; ICU: Intensive care unit; Stability day: The number of days from admission to clinical stability

phosphokinase (CPK) (418 vs 127.5, p=0.01) than those with simple influenza infection (tab. 3).

Laboratory evidence of bacterial infection was not identified, although sputum and blood cultures were performed on all patients with pneumonia. Urine antigens for *Streptococcus pneumoniae* and *Legionella* were negative in all patients. No other respiratory virus or atypical bacteria were identified. A possible explanation for this may be that 46% of the patients with pneumonia had received antibiotics for 24–48 hours before admission.

Regarding outcomes, the length of hospital stay (LOS) and was similar among patients from both groups and there were no deaths.

On multivariable analysis, smoking habit and elevation of serum LDH levels both appeared to be prognostic factors for the development of pneumonia as a complication of the influenza A H1N1 infection.

Outcomes

Following the WHO guidelines at that time, all H1N1 positive patients received oseltamivir (Tamiflu®) upon admission (75 mg bid for 5 days). The median time from illness onset to the initiation of antiviral therapy was 3 days (range 0–7 days); 12 patients (21%) had received antiviral therapy at the onset of symptoms. The median day of clinical stability for all the patients was 3.02 days (SD 1.7). All the patients with pneumonia received antibiotics and antiviral therapy.

The main reason for admission to the ICU was acute respiratory distress syndrome (ARDS) in 4 of the 7 patients (57%) and respiratory failure, myocarditis and pneumothorax each in one patient. No patient died.

DISCUSSION

To the best of the authors' knowledge, this is the first report on patients hospitalized due to the novel influenza A (H1N1) 2009 virus infection during the first wave (3 months) of the pandemic, in Greece. The Athens Chest Hospital "Sotiria" is the largest Greek tertiary care and national reference center devoted to respiratory diseases.

The epidemiological and clinical characteristics are described of the first 58 hospitalized patients with laboratory confirmation of influenza A (H1N1) infection, and in particular the subgroup of these patients (28/58) with pneumonia at the time of diagnosis.

Approximately 35% of laboratory confirmed cases reported recent return from vacation trip, analogous to other European countries in which the majority of confirmed cases

were travelers from Mexico and the United States.^{4,5}

The age distribution in the patients with influenza A (H1N1) infection was quite different from that of seasonal influenza,¹² with young adults bearing the heaviest burden and older people not very strongly affected. Possible explanations for this phenomenon include the fact that children are more likely to be exposed in schools and playgrounds and young people have a greater susceptibility to the virus (as compared to persons >60 years of age), on the basis of serologic studies.^{13–15} Additionally, young, febrile patients are more likely to be tested, since older adults with influenza often do not have fever.¹⁶ The mean age in this series of patients was 30.8 years which was higher than that reported by other European countries.³

Adult patients who are considered at highest risk for severe complications of influenza A (H1N1) are likely to include adults up to 65 years of age, or older adults of any age with underlying chronic medical conditions, immunosuppressed patients and pregnant women.^{8,9}

Asthma and COPD were the most common underlying conditions observed in the patients with pneumonia (42%). This finding is the same as in the cases reported by Perez-Padilla et al.⁶ Studies from the US^{18–20} indicated that obesity was a risk factor for severity of the disease and death. In this series only two of the patients with pneumonia were overweight, so obesity was not the most important factor for the severity of the disease.

The clinical spectrum of novel influenza A (H1N1) infection has already been defined.^{1,3,12} Both self-limited illness and severe outcomes, including respiratory failure and death, have been observed among patients with laboratory confirmed infection. The clinical features of cases reported here at the beginning of the pandemic closely resemble those in the data presented by other European countries (e.g. United Kingdom,⁴ Germany⁵) with fever, cough and myalgias being the most frequent clinical symptoms. Diarrhea and or vomiting were features of 26% of patients in this series, as in the study of Jain from USA,¹ but not in the Greek epidemiological study of Lytras et al.²

The risk factors for severe H1N1 respiratory illness, especially pneumonia, are still unclear, but most of the patients in this series were young to middle-aged and had previously been healthy. The pneumonia patients were older, more frequently had dyspnea and delayed admission to the hospital (3.7 vs 2.3 days). The most consistent laboratory characteristics statistically associated with pneumonia due to H1N1 virus were increased levels of LDH and CPK, in agreement with the results of Perez-Padilla et al⁶

and Hui et al.⁷ Unlike Perez-Padilla et al.,⁶ leucopenia was found in 34% of the patients in this series, and increased levels SGOT, which were statistically associated with the presence of pneumonia.

In this series, a significant proportion of hospitalized patients had chest X-ray findings consistent with pneumonia, and 43% of them had multilobar involvement. The exact cause of pneumonia cannot be easily determined solely from X-rays. It is apparent from the time interval between the onset of symptoms and hospital admission that the pneumonia is due to the primary infection with the influenza virus. Further studies are needed to correlate radiographic findings with the cause of pneumonia during influenza outbreaks.

Multivariable analysis demonstrated that the smoking status was correlated with pneumonia, possibly because of its negative effect on lung immunity, and elevated serum levels of LDH, expressing alveolar damage, were prognostic of pneumonia.

In terms of mortality, CDC reported that 29% of the fatal cases in USA presented at least one bacterial co-infection.²⁰⁻²² No evidence of bacterial co-infection was found in the present series, and there were no fatalities.

This study has several limitations. Firstly, the patients evaluated represent only one tertiary reference hospital for H1N1 infection in Greece. Secondly, only patients with a laboratory confirmation of influenza A (H1N1) 2009 infection were evaluated, so the group may not be representative of hospitalized patients who may not have been tested. Finally, the data were gathered early during the pandemic in Greece, and the findings may have been different during later waves, following the timely deployment of an effective vaccine, but also viral mutation, and development of resistance to antiviral drugs.

In conclusion, the patients with pneumonia and confirmed H1N1 infection are older than those with the simple H1N1 infection, and are more hypoxemic. The laboratory finding statistically associated with pneumonia due to H1N1 virus is the high serum level of LDH, and the smoking habit appears to be a risk factor. The findings of this study indicate that during such an epidemic, patients with pneumonia could be diagnosed sooner with the help of clinical and laboratory markers, in order to be managed appropriately and avoid ICU admission. Further studies are under way in all over the world to elucidate other potential risk factors for identification the severity of H1N1 infection in order to guide targeted management decisions.

ΠΕΡΙΛΗΨΗ

Προκαταρκτική ανάλυση νοσηλευόμενων ασθενών με γρίπη H1N1 σε Πανεπιστημιακή Κλινική, από το Μάιο–Αύγουστο 2009, στην Αθήνα

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ΣΚΟΠΟΣ Τον Απρίλιο του 2009, τα πρώτα περιστατικά του νέου τύπου της γρίπης Α (H1N1) καταγράφηκαν στο Μεξικό και από τότε ο ιός εξαπλώθηκε σε όλον τον κόσμο δημιουργώντας μια πανδημία. Σκοπός της μελέτης ήταν η περιγραφή των κλινικών χαρακτηριστικών και της εξέλιξης της νόσου των πρώτων νοσηλευόμενων ενηλίκων με αποδεδειγμένη λοίμωξη από ιό H1N1 σε ένα από τα κέντρα αναφοράς της Αθήνας και η διερεύνηση των παραγόντων κινδύνου για ανάπτυξη πνευμονίας από H1N1. **ΥΛΙΚΟ-ΜΕΘΟΔΟΣ** Χρησιμοποιήθηκαν αναδρομικά για συλλογή δεδομένων οι ιατρικοί φάκελοι των νοσηλευόμενων ασθενών. Η λοίμωξη από τον ιό H1N1 πιστοποιήθηκε σε φαρυγγικά δείγματα με τη χρήση της εξέτασης αληθούς χρόνου ανάστροφης αλυσιδωτής αντίδρασης τρανσκριπτάσης-πολυμεράσης (RT-PCR). **ΑΠΟΤΕΛΕΣΜΑΤΑ** Από 15 Μαΐου έως 15 Σεπτεμβρίου 2009, η πλειοψηφία (52%) των 58 νοσηλευόμενων ασθενών με λοίμωξη H1N1 παρουσιάστηκε με γριπώδη συμπτώματα και ήπια εξέλιξη. Περίπου 30% των ασθενών είχαν ένα ή περισσότερα συνυπάρχοντα νοσήματα. 28 από τους 58 ασθενείς (48%) παρουσίασαν πνευμονία, ενώ 7 από αυτούς νοσηλεύτηκαν σε μονάδα εντατικής θεραπείας. Τέσσερις από αυτούς τους ασθενείς παρουσίασαν ARDS και χρειάστηκαν μηχανικό αερισμό, με μηδενική θνητότητα. Οι ασθενείς με πνευμονία ήταν μεγαλύτεροι (36 έναντι 26, $p=0,003$), με βαρύτερη υποξυγοναιμία (39% έναντι 7%, $p=0,01$) και υψηλότερα επίπεδα ορού των SGOT (43,2 έναντι 25,5, $p=0,01$), CPK (418 έναντι 127,5, $p=0,01$) και LDH (345 έναντι 171, $p=0,002$) από τους υπόλοιπους νοσηλευόμενους με H1N1-λοίμωξη ασθενείς. **ΣΥΜΠΕΡΑΣΜΑΤΑ** Κατά την περίοδο της έρευνας (Μάιος–Αύγουστος 2009), ο ιός

της γρίπης H1N1 προκαλεί πνευμονία ανεξάρτητα από τη μικροβιακή λοίμωξη με προγνωστικούς παράγοντες για την ανάπτυξή της τα υψηλά επίπεδα LDH ορού και το κάπνισμα.

Λέξεις ευρητηρίου: Αθήνα, Ασθενείς, Γρίπη H1N1, Νοσηλεύόμενοι

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