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Full Length Research Paper

Clinical and health characteristic of patients diagnosed with Influenza A H1/N1 2009 and admitted in the respiratory unit of the area five hospital in the community of Madrid

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We have performed an epidemiological analysis of adult patients hospitalized with influenza A/H1N1 in the year 2009 in the Pulmonology Service of La Paz University Hospital in Madrid, Spain. We carried out a retrospective cohort and descriptive study in La Paz University Hospital from July to December 2009 of 102 patients diagnosed with Influenza A in the first 24 h of their stay in the Emergency Unit. All patients included in this study were those who were admitted in the Pulmonology Service. We did not include patients who died in the Intensive Care Unit (ICU).There included 45 women (44.12%) and 57 men (55.88%) with a mean age of 41.40 ± 1.67 years. The mean days of hospital stay was 6.20±1.02 days. Among the comorbidities, the most frequents were inmunossupresion, neoplasia and diabetes mellitus. The predominant symptomatology was cough, expectoration, fever and myalgia. In three cases, the patient was pneumococcical pneumonia. Radiograph abnormalities were found in 43 patients (45.26%) with diagnosis of Influenza 2009 H1N1. It was detected in 35 (36.84%) patients an alveolar pattern and other patterns were found. We think that this epidemic viral flu by H1N1 has permitted to know that viruses can be an important problem in the world health.

Key words: Influenza H1N1 2009 flu, epidemiology, comorbidity, thorax radiology.

INTRODUCTION

March and April 2009 will be remembered worldwide for the pandemic caused by a new strain of flu virus called 2009 A/H1N1. It is discussed where the virus appeared for the first time. Influenza viruses are members of the Orthomyxoviridae family, which is composed by five genera: Influenzavirus A, Influenzavirus B, Influenzavirus C, Isavirus and Thogotovirus. Virions are pleomorphic and have remarkable heterogeneity and antigenic variability that explain for the most part, why the influenza is still an important epidemic disease. Antigenic variation, primarily, is due to the two outer surface viral glycoproteins HA and NA. The existences of point mutations in them are responsible for annual epidemics

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of influenza. The genetic changes are caused by a more radical change in HA and / or NA Influenza A proteins and are usually associated with the emergence of new Influenza pandemics (Viasus et al., 2010; Viejo Bañuelos et al., 2010; Robert and Belshe, 2005).

The three major viral pandemic of the twentieth century were the 1918 Spanish flu, the 1957 Asian flu and the 1968 Hong Kong flu, H1N1, H2N2 and H3N2, respectively. All of them were characterized by a wide and rapid spread throughout the world, but only the Spanish flu reached a global mortality of 100,000 people (Seema et al., 2009).

Influenza A/H1N1 in 2009 was characterized by the presence of atypical pneumonia with bilateral radiograph opacities, increased lactate dehydrogenase serum concentration, absence of leukocytosis, lymphopenia, and sometimes increase of the creatine kinase (Cantaro Caballero et al., 2010; Cilla and Pérez-Trallero, 2010; Paño Pardo et al., 2011; Pérez-Padilla and Torre-Bouscoulet, 2009; Ajlan et al., 2009). It is important to stress that it was more prevalent in patients aged 20 to 40 years with a mortality rate of 0.71% (Saxena et al., 2009), in contrast to seasonal flu that has a different age distribution and higher mortality rates among the elderly (Chowell et al., 2009). Also, the beginning of the epidemic was atypical because it was during the spring and summer months (Chowell et al., 2009). The difference in the age distribution compared with seasonal flu can be explained because people exposed to influenza A/H1N1 who were born before 1957 had certain degree of protection and therefore a lower mortality rate (Chowell et al., 2009).

Symptomatology reported by patients ranged from a mild flu to respiratory failure and death (Ajlan et al., 2009). The radiological findings ranged from absent of radiological changes to unilateral or bilateral involvement that could be focal, multifocal or diffused with the presence of ground glass opacities, consolidations or interstitial distribution (Ajlan et al., 2009).

In this study, our aim has been to analyze the epidemiological informations of adult patients hospitalized with influenza A/H1N1 in the year 2009 in the Pulmonoogy Service of La Paz University Hospital in Madrid, Spain.

PATIENTS AND METHODS

Demography, patients and study design

We carried out a retrospective cohort and descriptive study in La Paz University Hospital from July to December 2009 of 102 patients diagnosed with Influenza A in the first 24 h of their stay in the Emergency Unit and that subsequently required admission in the Respiratory Unit or the Intensive Care Unit (ICU) of our hospital. All patients included in this study were those who were admitted in the Pulmonology Service, coming from the Emergency Unit, ICU or others Services of the Hospital. We did not include patients who died in the ICU, if they were not before in the Pulmonology Department.

Data of patients was collected from their medical record and from the data file required by the Health Ministry in order to archive all information regarding Influenza A.

We collected the following data: date of hospital admission, age, sex, nationality, presence or absence of pneumonia on the first chest radiograph, reason for admission in the Pulmonology Service, date of admission and of discharge and days of hospital stay. Similarly, concerning admission to the ICU, length of stay and if mechanical ventilation was needed. We investigated the existence of contact with someone infected or possibly infected with influenza A H1/N1, and the comorbidity of patients (cancer, diabetes, immunodeficiency, heart disease, prior lung disease, epilepsy, malnutrition, others ...).

Screening for H1N1 infection was performed in all patients that had symptoms compatible with this disease and any comorbidity, other respiratory infectious disease or any medical complication. Diagnosis was performed by microbiology confirmation using polymerase chain reaction in real time (PCR-RT) according to the CDC protocol for the detection of Influenza A virus H1N1, as was recommended by the Health Ministry. In some cases, when the clinical suspicion was high and the first microbiology screening was negative, the test was repeated one more time. As a rule, the microbiology results were obtained within the first 24 h and, usually within the first 12 h. Confirmed cases were defined as any person with compatible symptoms with H1N1 infection and microbiology confirmation, defined by the PCR-RT test positive or nasopharyngeal, throat or lower respiratory tract sample culture positive in selected cases (only performed in patients admitted to the ICU).

We excluded in this study children, that is, patients admitted to the ICU who after were not referred to the Pulmonology Service (because they died in the ICU) and pregnant women section.

The study was approved by the Scientific Research Ethics Committee (CEIC) and has kept all the Data Protection measures specified by Law 15/1999.

Clinical evaluation and follow up

We have performed a radiological study which compared the image findings of patients with influenza A/H1N1 2009 with those of a control group formed by patients attended in the emergency department with respiratory symptoms related to seasonal flu and that required chest radiograph. The evaluation of the control group was performed retrospectively and included only patients attended in January 2009 corresponding to the peak of seasonal flu and before the first outbreak of Influenza A. There were excluded in the control group all patients with positive serological results to *Mycoplasma pneumoniae, Legionella pneumophila, Coxiella burnetii, Chalmydias* sp and other respiratory microorganisms. Also, patients with positive blood and sputum culture and positive baciloscopy were excluded.

We evaluated the following radiological features: radiological patterns: alveolar, interstitial, mixed; distribution of the images: segmental bronchial, lobar, patchy (in more than one area, separated by areas not affected); location: bilateral or diffuse and the number of non-contiguous segments or areas affected; other information: pleural effusion, lymphadenopathies, hypo-ventilation, laminar atelectasis...

Procedure: initial chest radiography was performed using the standard method. All radiological examinations were evaluated by two radiologists by consensus, one expert in chest radiology and the other expert in emergency radiology.

Statistical analysis

We have used the SPSS system to analysed our data. Data

were described as mean ± standard deviation or percentages. The comparisons were done with the Student´s t test for variable with normal distribution and the Mann-Whitney´s U test for variables with non-normal distribution. We consider significant $p<0.05$.

RESULTS

We have analyzed a total of 102 patients admitted in the respiratory unit between July and December 2009. There were included 45 women (44.12%) and 57 men (55.88%) with a mean age of 41.40 ± 1.67 years. The mean days of hospital stay was 6.20 ± 1.02 days.

When analyzing comorbidities, we found six cases of neoplasia (5.88%), seven cases of Type 2 diabetes mellitus (6.86%), eleven cases with immunosuppression (10.87%), eight cases with heart disease (7.84%), three with epilepsy (2.94%) and twenty with previous lung disease (19.61%), of which six were diagnosed with COPD and fifteen with asthma. Asthma attack was the respiratory disease most associated with ICU admission. 22 patients (21.57%) were smokers and 20 patients (19.61%) had different comorbidities such as morbid obesity. Five patients (4.90%) did not have any pathological history (Figure 1).

When we had analyzed the reasons for patient's hospitalizations we had observed that 44 patients (43%) were diagnosed with pneumonia although only in 25 of them (24.50%), pneumonia was the real indication for admission. The other reasons for hospitalization were respiratory sepsis (4.9%) in five cases, immunodeficiency in six cases (5.88%), respiratory failure in 35 patients (34.35%), bronchospam in seven cases (6.86%) and 24 cases (23.50%) were admitted for other reasons (Figure 2).

The patient's symptomatology is presented in Table 1. Most common symptoms were: fever in 93 patients (91.17%), cough in 78 (76.47%), expectoration in 55 (53.92%), myalgia in 52 (50.98%), dyspnea in 39 (38.23%), chest pain in 32 (31.37%), asthenia in 61 (59.80%) and nausea and vomiting in 42 (41.17%). Many patients had various symptoms concomitantly.

In the analysis of the microbiology, we found pneumococcal pneumonia in three patients (2.94%), and also, we have diagnosed pneumonias caused by other bacteria like *Pseudomonas aeruginosa* in one case (0.98%), *Klebsiella ozonae* pneumonia in one patient (0.98); *C. burnetii* in two patients (1.96%) and *Stenotrophomonas maltophilia* in one case (0.98%). Bacteremia was detected only in one case and was due to *Staphylococcus aureus* and all the sputum baciloscopy were negative.

There were no deaths in the respiratory unit. All patients were treated with Tamiflu® (Oseltamivir) and transaminases were elevated up to the normal range in 10 cases (9.80%) but only in two patients it forced to withdraw the drug with subsequent normalization of the hepatic enzymes. All patients that were hospitalized also were treated with broad-spectrum antibiotics.

Monthly distribution of confirmed cases was not uniform and the highest number of cases were found in the months of October and November (44 (43.14%) and 34 (33.33%), respectively). There was one (0.98%) case in July, five (4.90%) in August, six (5.88%) in September and finally, two (1.96%) in December (Figure 3).

Eighteen patients (17.65%) were transferred to the ICU from the urgency unit, and three (16.67%) of them died (one patient with COPD Stage IV, a patient diagnosed of ovarian malignancy Stage IV and another patient with acute respiratory failure and respiratory distress produced by the virus,). The other patients did not have any complication and were transferred to the respiratory unit. No patient admitted in the respiratory unit presented any complication or required subsequent admission to ICU.

Parallel to the clinical study, a radiological study was carried out with the aim to study and compare the findings of initial chest radiographs of the first 95 patients diagnosed with influenza 2009 A/H1N1 [50 (52.63%) males and 45 (44.12%) women], with a control group of 98 patients diagnosed of seasonal flu and retrospectively studied in January 2009, before the first outbreak of influenza A H1N1 virus.

Radiograph abnormalities were found in 43 patients (45.26%) with diagnosis of Influenza 2009 H1N1. It was detected in 35 (36.84%) patients an alveolar pattern (Figure 4): 18 (18.95%) had patchy consolidation, 12 (12.63%) had segmental infiltration of bronchial distribution and five cases (4.90%) had lobular involvement. Seven (7.37%) patients had an interstitial peribronchovascular pattern and only one case (1.05%) had a reticulonodular interstitial pattern. Similarly, pleural effusion was found in seven (7.37%) patients. There was a predominance of lower lobe involvement [(right inferior lobe in 18 people (18.95%) and left inferior lobe in 24 (25.26%)] and bilateral spread was observed in 20 (21.05%) patients.

By contrast, in the control group there were significant radiological findings in 41 patients (41.83%). It was described an alveolar pattern in 39 patients (95%) of those affected (two (5%) with focal patchy distribution, 18 (46%) with lobular and 19 (49%) with segmental infiltrates), a mixed alveolar-interstitial pattern in one patient (2.5%) and a reticulonodular interstitial pattern in another patient (2.5%). The radiograph findings were presented in the: right upper lobe in one patient (2.5%), left upper lobe in four cases(9.75%), middle lobe in four patients (9.75%), right lower lobe in 15 cases (36.58%) and left inferior lobe in 17 patients (41.46%). The total number of lobes affected was one in 29 cases (70.73%) and two in 12 patients (29.27%). No patient had more than two lobes affected. In four (9.75%) cases we identified a small amount of pleural effusion. Three patients (7.32%) showed hypoventilation areas or laminar

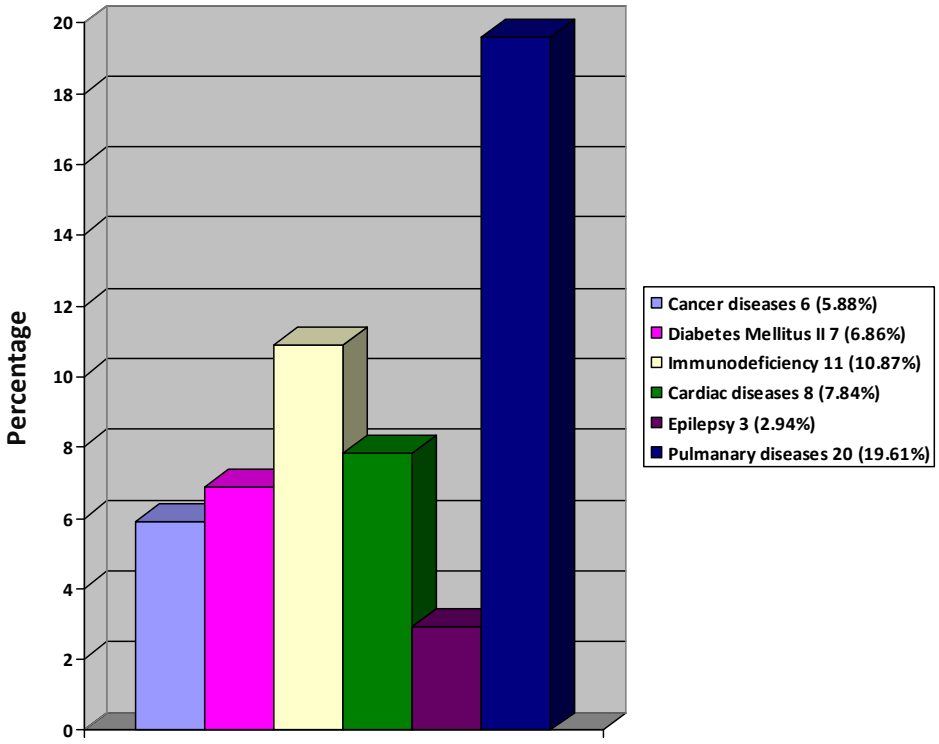

Figure 1. Personal antecedents.

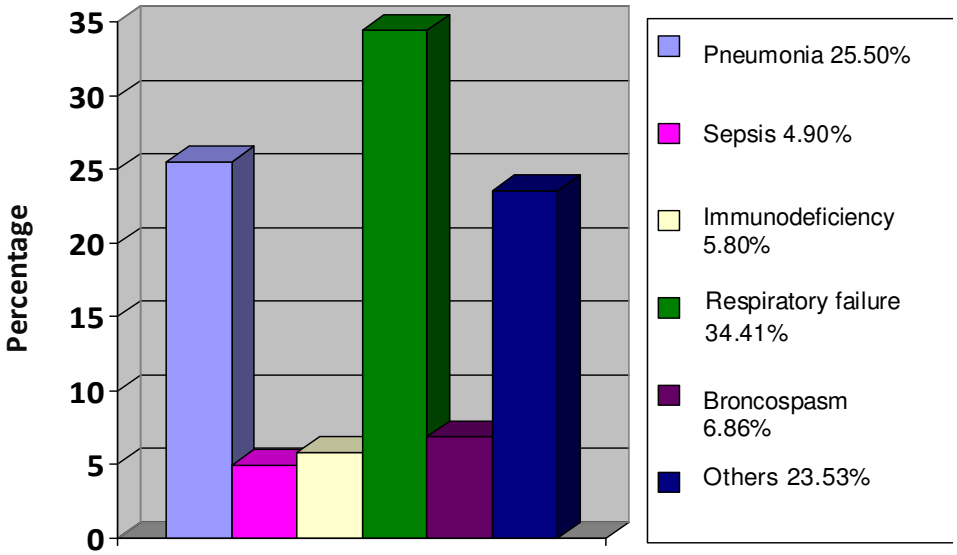

Figure 2. Etiology.

atelectasis. No lymphadenopathy was detected in any patient in this group.

We found significant differences between the mean age of patients with influenza 2009 A/H1N1 with the control group (mean 40.20 vs. 50.90 years, p <0.001). The most common radiological findings in the influenza A/H1N1 group was multifocal patchy alveolar pattern, that was significant different compared with seasonal flu group(p <0.001) (Figure 5).

DISCUSSION

Human to human transmission of Influenza A/H1N1 2009

Table 1. More frequent symptoms.

Symptoms	Number and percentage
Fever	93 (91.17%)
Cough	78 (76.47%)
Expectoration	55 (53.92%)
Muscular pain	52 (50.98%)
Dyspnea	39 (38.23%)
Thoracic pain	32 (31.37%)
Asthenia	61 (59.80%)
Odynophagia	25 (24.50%)
Effusive perspiration	7 (6.86%)
Nausea and vomiting	42 (41.17%)
Diarrhea	14 (13.72%)
Headache	31 (30.39%)
Rhinorrhea	9 (8.82%)

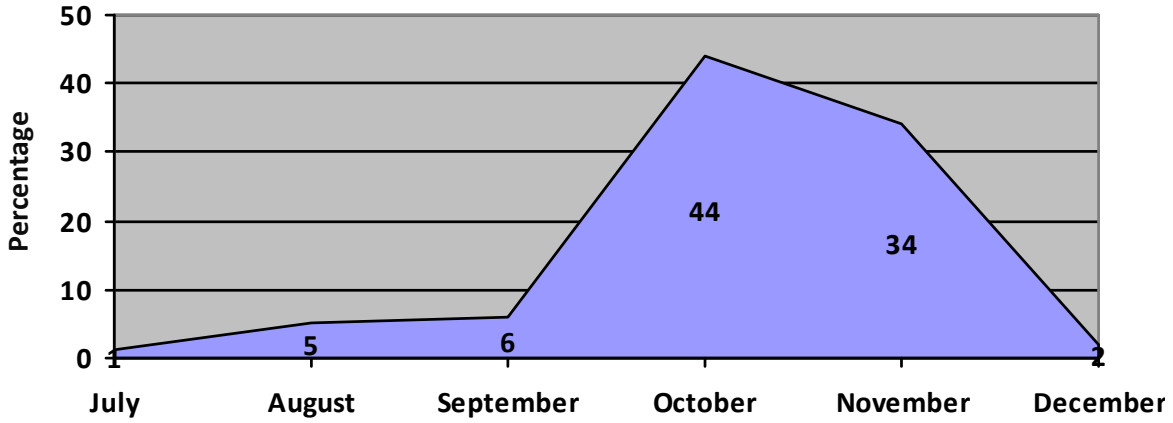

Figure 3. Distribution of patients.

was similar to the human seasonal flu, by droplets through the coughing and sneezing of patients. The incubation period, as shown in other studies, ranged from one to seven days (Ajlan et al., 2009). People affected by this virus were younger in contrast to seasonal flu (Ajlan et al., 2009). In our study, patients were aged between 15 and 50 years (70.6%), with a mean age of 41.4 years; and only 30 patients were older than 50 years. Results from other no-Spanish studies are similar, where the age of patients affected ranged from 13 to 47 years (Pérez-Padilla et al., 2009). The results described of the 1918 flu or the avian influenza H5N1 are very similar. In our center the month distribution of the epidemic was similar than that of the global epidemic, (Figure 3), no corresponding to the seasonal flu epidemiology (Pérez-Padilla and Torre-Boucoulet, 2009).

Factors associated with severe lung disease or with an increased risk of infection by this virus were the age, chronic comorbidities and bacterial superinfection. There is enough evidence that indicates that the influenza virus affects the host's inflammatory response and predisposes to its adherence, its invasion and the presence of diseases caused by bacterial organisms (Fitzgerald, 2009). In fact, during the influenza pandemics of the twentieth century, bacterial infections superimposed on the viral illness were associated with a large number of deaths, being *Streptococcus pneumoniae* the most common etiology (Morens, 2008). However, according to the results of some studies performed in the last pandemic, concurrent bacterial infection does not appear as the principal factor associated with the severity of the disease, probably because most patients had concomitant antibiotic therapy, as occurred in our series (Morens, 2008). This would explain the lower frequency of radiographic alveolar pattern that is compatible with bacterial super infections. In some studies it was suggested that there were differences between the epidemiological findings of this infection and those of

Figure 4. Thoracic radiography: bilateral alveolar pattern, more in the lower lobes.

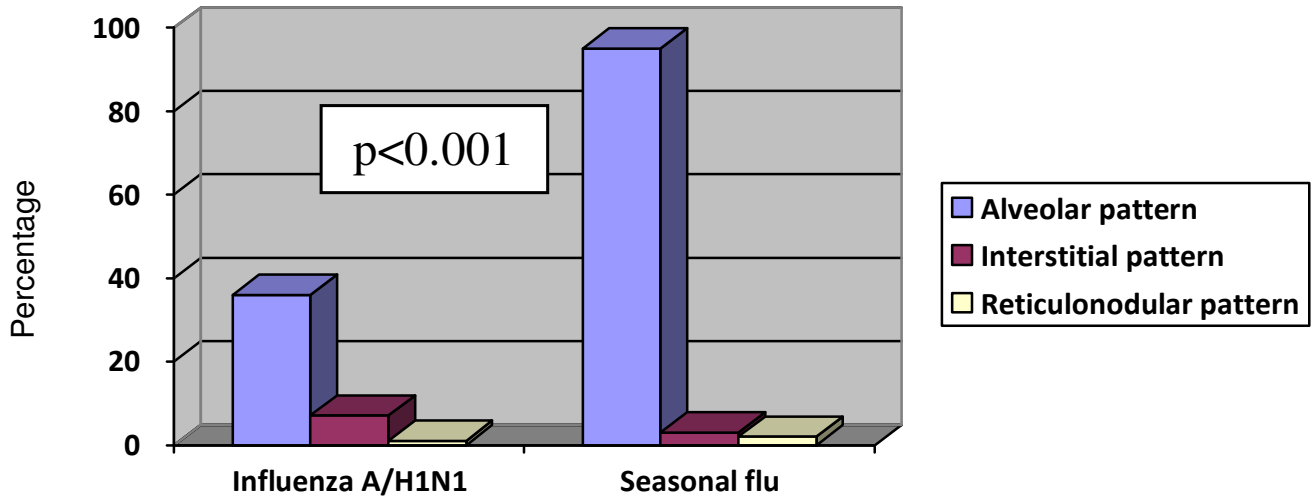

Figure 5. Comparation of the radiological findings between Pandemic flu 2009 and seasonal flu.

community-acquired pneumonia (CAP) so that the influenza H1N1 2009 affected younger people and caused more severe respiratory compromise than CAP (Steen et al., 2010a).

In our study, demographic characteristics of patients diagnosed with Influenza A were similar to those of other hospitals in the Community of Madrid and of other Communities, both in the age and sex distribution,

although our patients were men predominantly (Steen et al., 2010a; Mínguez Clemente et al., 2010; López Reyes et al., 2010; Selma et al., 2010; Mella Tejeda et al., 2010; Piñeiro Martínez et al., 2010; Biteri Martínez de Iturrate et al., 2010; Padilla Galo et al., 2010; Vigil Vigil et al., 2010).

The mean hospital stay of patients admitted with the Influenza A/H1N1 infection in the Community of Madrid was 5.3 days, in our study it was slightly higher (6.2 days), probably because in our center most inpatients had any comorbidity (95.10%) and in other hospitals of the Community of Madrid the prevalence of comorbidities ranged from 70 to 80% (Steen et al., 2010a; Mínguez Clemente et al., 2010; Padilla Galo et al., 2010; Villar Álvarez et al., 2010). In our study, 100% of patients were admitted to the respiratory unit, so its organization was adapted to the number of admissions, something not common in other hospitals of the Community of Madrid (Villar Álvarez et al., 2010).

As in another series, we have observed a high prevalence of comorbidities (80% of patients) and respiratory diseases were the most important entities seen in these patients (Steen et al., 2010a,b; Mínguez Clemente et al., 2010; Villar Álvarez et al., 2010). Chronic obstructive pulmonary disease (COPD), and asthma were the diseases most often associated with Influenza H1/N1 infection and also, they were a risk factor for ICU admission (Steen et al., 2010b). Compared to other hospitals of the Community of Madrid, we had found a higher percentage of admissions in the ICU (17.24%), although mortality was lower than that observed in all the Community (0.07%) (Steen et al., 2010b). It was reported that there was a high prevalence of obesity among patients infected with influenza A, amid a prevalence between 45 and 90% of obesity among these patients in the U.S. (Agarwal et al., 2009). In our study, this finding was evident but in a smaller percentage (less than 19.67%). Although obesity has not been clearly established as a risk factor for the development of influenza, an important association to investigate in the future could exist. We did not find any risk factor associated with poor infection prognosis (Pérez-Padilla et al., 2009; Kotsimbos et al., 2009). Concerning this, investigations in serum biomarkers have concluded that procalcitonin could be a useful tool to know the etiology and prognosis of Influenza 2009 A/H1N1 infection, even in association with other concomitant infections (Pando Sandoval et al., 2010).

Recent studies have showed that the early administration of antiviral drugs is associated with favorable outcomes, mild disease, and less development of respiratory failure (Fitzgerald, 2009). All patients received oseltamivir with a favorable outcome of the disease, and only few complications of little severity. Although there is evidence concerning the benefits when antiviral therapy is initiated before the first 48 h after the start of symptoms, this treatment is also recommended after this period, especially in hospitalized patients with comorbidities, in which there are an increased risk of complications (Fitzgerald, 2009). Most cases of associated pneumonia were diagnosed prior to the confirmation of Influenza A/H1N1 and to the initiation of therapy with Tamiflu® (oseltamivir). In cases where no bacterial superinfection appeared after starting antiviral treatment, concomitant antibacterial treatment was initiated in all cases (Morens et al., 2008). As was reported in Mexico, the delay in beginning antiviral drugs is associated with an increased mortality (Pérez-Padilla et al., 2009). The withdrawal of antiviral therapy due to serum transaminases elevation occurred in two cases, with improvement after discontinuation of the drugs. In the other cases with serum transaminases elevation, doubt remains about whether this increase was due to treatment or to disease itself, as it has been reported an association between serum transaminases elevation and viral infection in some cases.

In our study, we found that about 50% of patients admitted with this infection had radiographic changes in the initial chest radiograph, which were not specific, and appeared at a lower frequency than in the seasonal flu, and principally was observed a patchy multifocal alveolar involvement as was in other studies (Ajlan et al., 2009; Agarwal et al., 2009).

As reported by Perez Padilla and Torre-Bouscoulet (2008), the Influenza virus H1N1 2009 is not the only protagonist. It is also an important host in the environment, including the social environment. We have to remember that there was fear for the virus and for the infection, and that this infection occurred in a susceptible population.

As in all the other reports, we have found a lower mortality rate and severity grade than initially was expected (Kotsimbos et al., 2010).

Concerning limitations, we have only included patients admitted in the respiratory unit of our hospital. There are therefore excluded of the study outpatients, children, pregnant women and patients admitted in the ICU who died.

It would be interesting to compare this data with a greater number of hospitals not only from Spain, in order to perform an exhaustive investigation of the performance of this respiratory infection.

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