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Original Article

Impact of the A (H1N1) pandemic influenza (season 2009–2010) on patients with cystic fibrosis

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Abstract

Background: Influenza, like other respiratory viral infections, can cause acute deterioration of lung function in patients with cystic fibrosis (CF). Previous studies on a small number of patients reported that most people with CF infected with A (H1N1) influenza experienced a mild course of disease.
Aim: To characterise the impact of A (H1N1) infection on CF in a large number of patients from different centres and countries.

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Methods: CF centres accessing the web-site of the European Cystic Fibrosis Society (ECFS) were asked to report clinical data on patients with an ascertained diagnosis of influenza caused by the A (H1N1) virus. The study was web-based and data were collected through an electronic data sheet on the ECFS website.
Results: Twenty-five centres from 10 countries caring for 4698 patients with CF reported data on 110 patients (2.3%), median age 13 years (range 1–39 years). The prevalence of infection in each centre ranged from 0% to 9.4%. Only 8.8% of the patients had been vaccinated. The main symptoms were fever and respiratory exacerbation requiring IV antibiotics in 53% of the patients; 48% of the patients were hospitalised for an average of 12.9 days (range 2–56) and 31% required oxygen treatment during the time of the infection. Most of the patients recovered and FEV_1 1 month after the infection was similar to that before the infection. However, 6 patients were admitted to ICU, 5 with mechanical ventilation. Three patients with severe respiratory disease died.
Conclusions: A (H1N1) influenza infection caused transient but significant morbidity in most of the patients with CF. However, in a small number of patients with severe lung disease, A (H1N1) influenza was associated with respiratory deterioration, mechanical ventilation and even death.

Keywords: A(H1N1); Cystic fibrosis; influenza

1. Introduction

Pandemic 2009 influenza A (H1N1) is a new strain of influenza virus that was first identified in Mexico in March 2009 [1,2]. The World Health Organization's declaration of a pandemic of the novel A (H1N1) influenza virus raises questions regarding its potential morbidity and mortality. At first sight, the data seem to imply that this new virus is relatively mild, with case fatality ratios around 0.5%, which is similar to the upper range of that seen for seasonal influenza [3], and relatively low hospitalisation rates. However, the case:fatality ratio seems to vary substantially between countries, and deaths have occurred in much younger people than is the case for seasonal influenza [4]. As of July 2010, more than 214 countries and territories or communities worldwide have reported laboratory confirmed cases of A (H1N1) influenza, including over 18,398 deaths [5]. The Centers for Disease Control and Prevention (CDC) estimate that in the period April 2009–April 2010 ~61 million cases occurred in the US, ~274,000 cases were hospitalised and ~12,470 cases died [6]. The majority of patients with pandemic A (H1N1) influenza infection developed mild upper respiratory tract symptoms similar to seasonal influenza. However, from the beginning of the pandemic, reports of deaths associated with A (H1N1) influenza infection were reported [7–9]. A weekly surveillance of severe acute respiratory illness conducted by the European Centre for Disease Prevention and Control (ECDC) ascertained a cumulative number of 11,593 cases with 575 deaths in 11 countries, corresponding to an incidence of fatal cases in the population ranging from 0.17 to 1.05 per 100,000 [10] .

In contrast to seasonal influenza, many of the severe pandemic A (H1N1) influenza cases and their related mortality have occurred among children and young adults, and about 40% of the patients that required hospitalisation or died were previously healthy [11,12]. A study from Argentina reported that the hospitalisation rate for 2009 A (H1N1) influenza among children was twice that for 2008 seasonal influenza in the same population [4]. In the US, the rate of death was 10 times the rate associated with seasonal influenza for the same population in 2007 and 5 times the rate reported by the CDC for the US paediatric population during the relatively severe 2003–2004 influenza season (0.2 deaths per 100,000 children) [13]. Mortality was particularly high among infants (7.6 deaths per 100,000 children), which was 10 times the US infant death rate from seasonal influenza in 2003–2004 [13]. Most deaths were attributable to refractory hypoxemia.

Influenza, like other respiratory viral infections, can cause acute deterioration of lung function in patients with cystic fibrosis (CF) [14]. Although vaccination is recommended, inadequate coverage has been reported [15,16]. Recent reports from Australia and the UK on a very small number of patients with CF infected with A (H1N1) virus reported a mild course of disease with complete recovery [17,18]. The present study was initiated when the World Health Organisation and the European health authorities declared the A (H1N1) pandemic. The aim of this study was to characterise the impact of A (H1N1) infection on patients with CF on a large number of patients from different centres and countries.

2. Patients and methods

Since a complete list of CF centres throughout Europe does not exist, we decided to publish a call describing the aims of the study on the ECFS web site (http://www.ecfs.eu). This web site is well established in the CF community and regularly visited. Through the web site the CF centres were asked to report patients infected with the A (H1N1) virus. The study was internet-based: participating centres were asked to register for the study and received a username and password to log in. Once registered, investigators had to enter CF-centre identification information (name of the centre director, name of the institution, city and country), provide an e-mail address for contact, and record the total number of patients followed in the centre. Data were uploaded through the web site of the CF Centre in Verona and were hosted in the hospital's server. Help desk was provided by an operator of the CF Centre in Verona.

Data were collected anonymously (patients were identified by codes known to the CF centre only). Diagnosis of A (H1N1) infection was determined by RT-PCR or by direct immunofluorescence, and/or by epidemiological criteria

(close contact with a person with laboratory confirmed A (H1N1) infection). Centres were asked to also report zero cases. The reporting period covered the A (H1N1) pandemic throughout Europe as described and followed by ECDC. Patients were recruited from July 2009 (28th week of 2009) to December 2009 and followed until April 2010.

The information collected included age and gender, genotype, pancreatic status, previous vaccination against A (H1N1) virus, date and method of A (H1N1) diagnosis of infection, symptoms and signs of flu, therapy of A (H1N1) infection and complications including intravenous antibiotic therapy, ICU admission and death. The initiation of intravenous therapy and decision for ICU admission were based on the clinical assessment of the treating physician at each centre. The effect on the clinical course of the patient was assessed by collecting information on pulmonary function (FEV_1), nutritional status (height and weight) and sputum culture before and after A (H1N1) infection.

We collected FEV_1 as absolute values for volume and used the equations from Hankinson et al. [19] and Wang et al. [20] to compute FEV_1% predicted values.

3. Statistical analysis

Results were summarised as proportions, and Chi-square test and Fisher's exact test were used to compare proportions across categories. The Cochran–Armitage test for trend was used to test whether the proportion of patients reporting symptoms increased linearly with age. McNemar test was used to assess whether there was a change in sputum culture before and after A (H1N1) infection. Statistical significance was considered at the level of $p<0.05$.

4. Results

A total of 25 CF centres from 10 countries participated in the study, caring altogether for 4698 patients (Table 1). Over the study period, 110 patients (2.3%; 95% CI: 1.9%; 2.8%) were diagnosed as infected with the A (H1N1) virus; the percent of infected CF patients in the various centres ranged from 0 to 9.4% of the total number of CF patients at each centre. The time course of the epidemic in CF patients (Fig. 1) was similar to that reported by the ECDC for the general population. The first case was reported on the 28th week and the last one on the 52nd week of 2009. Patients were diagnosed as having A (H1N1) by RT-PCR (85.5%) or by direct immunofluorescence (7.3%). In two cases diagnosis was based on epidemiological criteria (close contact with a patient with laboratory proven A (H1N1) influenza). Information on mode of A (H1N1) diagnosis was missing for 2 patients. Only 8.8% of the 110 patients had been vaccinated against A (H1N1) and 89 patients (81%) were treated with oseltamivir.

Table 1
Number of patients by centre and country participating in the A (H1N1) ECFS study group.

Country	No. of centres	No. of patients followed-up	No. of patients diagnosed with A (H1N1) infection (%)
Austria	1	40	1 (2.5%)
Belgium	5	793	27 (3.4%)
France	2	325	7 (2.2%)
Germany	1	150	2 (1.3%)
Israel	2	188	9 (4.8%)
Italy	9	2602	50 (1.9%)
Portugal	1	102	4 (3.9%)
Spain	2	219	6 (2.7%)
UK	1	175	2 (1.1%)
USA	1	104	2 (1.9%)
Total	25	4698	110 (2.3%)

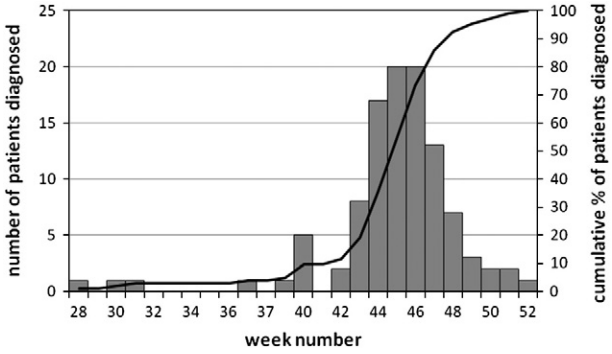

Fig. 1. Number of patients diagnosed with A (H1N1) infection in 2009, by week of diagnosis.

4.1. Clinical presentation

The median age was 13 years (range 1–39 years), and 32 patients were above age 18. Age distribution by gender is shown in Fig. 2. Of the 110 patients (55.5% males), 84% were pancreatic insufficient, 36 patients (35%) were homozygous for the F508del mutation, 50 (48.5%) were heterozygous and 17 (16.5%) did not carry the F508del mutation on either allele. For 7 patients genotype was not reported.

Presentation of A (H1N1) infection was characterised by the presence of fever in 94% of the patients, increased cough in 73%, increased sputum production in 54%, fatigue in 51% of the patients and sore throat in 34%. Five patients (4.5%) had haemoptysis. Reporting of increased sputum production increased with age from 17% in the age group 0–5 years to 69% in the age group ≥18 years (test for trend, $p<0.001$). Similarly, reports of fatigue increased with age (test for trend, $p=0.005$), from 33.3% of patients aged 0–5 years up to 69% of patients aged 18 years or older.

4.2. Morbidity and mortality

A (H1N1) infection had a significant impact on the disease course in patients with CF: 58 patients (53%) required intravenous antibiotic therapy, 53 patients (48%) were hospitalised for an average of 12.9 days (median: 12, range: 2–56) and 34 patients (31%) required oxygen treatment

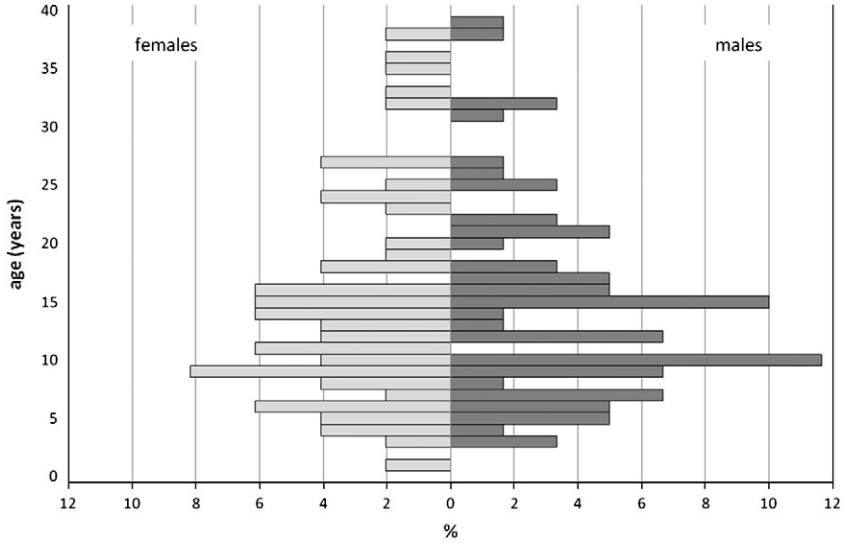

Fig. 2. Age distribution by gender of CF patients reported as infected with A (H1N1).

during the time of infection. Six patients (5.4%) required treatment in ICU (range: 1–21 days) and five (4.5%) required non invasive ventilation for 1–15 days. Three patients, all with previous severe lung disease, died. One of these patients was on the waiting list for transplantation before he was infected by A (H1N1); the other two had FEV_1 values below 30% and BMI of 16.9 and 19.1 kg/m^2.

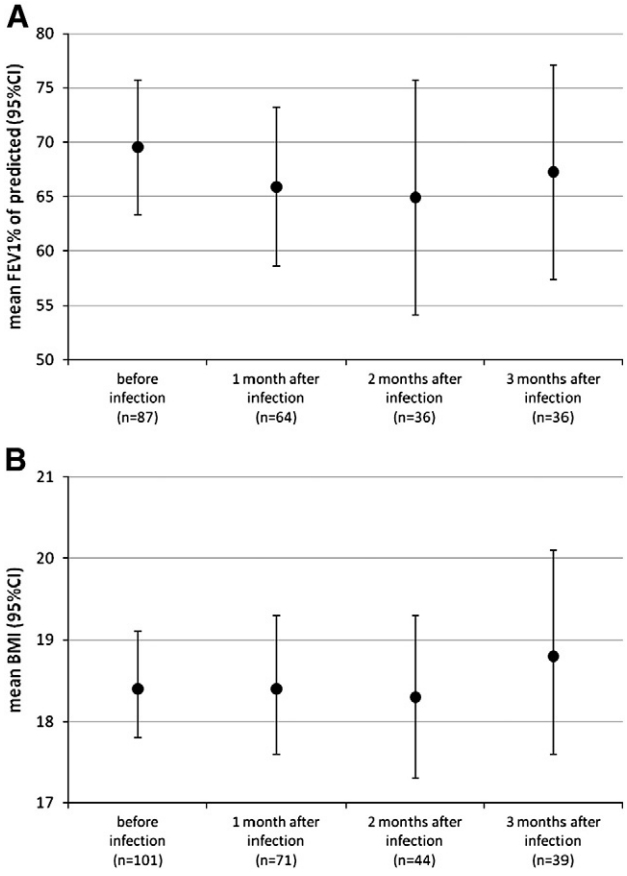

Fig. 3. FEV_1% predicted values and BMI in CF patients with A (H1N1) infection before and 1, 2 and 3 months after A (H1N1) virus infection.

4.3. Pulmonary function

Information on FEV_1 values before A (H1N1) infection was available for 87 of the 97 patients older than 6 years, and information on FEV_1 values 1 month after A (H1N1) infection was available for 64 patients. Fig. 3 (panel A) shows the mean FEV_1% predicted before A (H1N1) infection and 1, 2 and 3 months after infection. The mean FEV_1% predicted prior to A (H1N1) infection (69.5% predicted, 95% CI: 63.3; 75.7) was similar to 1 month after A (H1N1) infection (mean: 66% predicted, 95% CI: 58.6; 73.2). However, variable responses were observed among the patients: 3 patients had a decrease of at least 15 percent points, 5 had an increase of at least 15 percent points and 56 had a variation which was between 15 percent points decrease and 15 percent points increase. The level of FEV_1 prior to A (H1N1) infection did not correlate with the change in FEV_1 after A (H1N1) infection. It is important to note that FEV_1 values were not available for the patients that had severe deterioration, i.e. those that were admitted to ICU or died, and this could affect the results.

Patients who were hospitalised had prior to infection mean FEV_1% values that were significantly lower than those of patients not admitted (mean, 95% CI admitted: 60.3, 51.5–69.2; non-admitted: 78.1, 69.9–86.3). Patients with different BMI values (below and above 18 kg/m^2) showed similar FEV_1% values throughout the whole study period.

4.4. Nutrition

Information on BMI before A (H1N1) infection was available for 101 patients and for 71 patients also 1 month after infection. Mean BMI before A (H1N1) infection did not change 1 month after the infection: 18.4 kg/m^2 (95% CI: 17.8; 19.1) and 18.4 kg/m^2 (95% CI: 17.6; 19.3), respectively.

However, when we analysed variations in BMI according to pancreatic status, we found in pancreatic insufficient patients ($n=55$) an average decrease in BMI of 0.14 kg/m^2 (95% CI: −0.33; 0.05), $p=0.002$, compared with pancreatic sufficient patients. Fig. 3 (panel B) shows the mean BMI before A (H1N1) and up to 3 months after infection. As mentioned above for FEV_1, we did not have BMI values for the more severe patients; those that were admitted to ICU or died, and this could affect the results.

4.5. Bacteriology

There was no significant change in sputum culture growth in the overall group before and after A (H1N1) infection ($p=0.99$): 8/74 (10.8%) of patients free of *Pseudomonas aeruginosa* before infection were positive after infection, whereas 8/37 (21.6%) of patients positive for *P. aeruginosa* before infection were negative after infection.

5. Discussion

This study shows that infection with A (H1N1) caused considerable morbidity to patients with CF, with two-thirds of the patients requiring intravenous antibiotic therapy, half requiring hospitalisation and 30% needing supplemental oxygen treatment during the time of infection. The worst impact was on 6 patients, all with severe lung disease prior to the infection, which required treatment in ICU, five of them needing ventilation and 3 patients died during the course of the infection. Thus, in the present patient cohort, the majority of the patients had short term and transient symptoms with recovery to pre-infection status within 1 month. However, a few patients, all with pre-existing severe lung disease, were severely affected; some of them died after being infected by the A (H1N1) virus.

Recent reports demonstrated that hospitalised adults with A (H1N1) influenza infection were relatively young, and a significant number (up to 25%) required treatment in the ICU [21]. The epidemiology of fatal A (H1N1) cases in the United Kingdom (UK) demonstrated that, unlike seasonal influenza, fatal cases were mainly seen in young adults. Among patients that required ICU admission, most developed acute lung injury or acute respiratory distress syndrome and required mechanical ventilator support. Severe hypoxemia developing into ARDS with multi-organ dysfunction in the absence of bacterial infection was a common clinical presentation [22]. The mortality in these cases was high and was primarily due to refractory hypoxia. Again, it appeared that some individuals were predisposed to develop severe and even fatal disease as a result of A (H1N1) infection. Underlying risk factors for severe disease were chronic neurological disease, immunosuppression and respiratory diseases [23]. Other reported risk factors for severe disease and fatality were pregnancy and obesity [24,25]. A recent study from the UK demonstrated that the presence of chronic respiratory diseases other than asthma or COPD increased by an average of threefold the risk for critical care requirement or death of patients affected by A (H1N1) infection [26]. Due to the multicentre nature of the study, data on population morbidity during non-epidemic years could not be obtained and therefore could not be compared with current morbidity levels. Although ICU admissions involving CF patients are infrequent events the rate of ICU admission in the current study (5.4%) seems high.

Previous studies showed that respiratory viral infections significantly increased respiratory illness and rates of hospitalisation in children with CF [14,27–30]. Viral infections were shown to be one of the main mediators of the onset of chronic *P. aeruginosa* infection in CF [31]. Furthermore, a recent large epidemiological study demonstrated that the influenza season was associated with increased rates of CF pulmonary exacerbations [32].The findings in the current study on A (H1N1) influenza infection in CF are similar to previous reports of influenza A [14], showing deterioration in pulmonary function and BMI in only some of the patients. Interestingly, we did not find a change in the *Pseudomonas* status in patients in the first 3 months after A (H1N1) influenza. It is likely that some patients are prone to develop severe deterioration, especially those with severe lung disease and patients with impaired immune response to viral infections. It was recently shown that various host innate immune responses to different influenza virus subtypes, or viral haemagglutinin titres, might be associated with disease severity [33].

To the best of our knowledge, this report is the first multinational study describing a large group of patients with CF with laboratory confirmed diagnosis of A (H1N1) influenza infection, covering 25% of the European CF patient population as recorded in the ECFS Patient Registry [34]. The overall time course of the A (H1N1) epidemic in CF patients described here followed the same pattern as observed in the general population, showing the highest intensity between week 40, 2009 and week 1, 2010, peaking at week 46, 2009. After this date, for the following 8 weeks, all reporting countries experienced low intensity with only sporadic cases [10].

Age distribution peaked in the paediatric age and the number of adult patients (≥18 years) was lower than expected: only 29.3% versus 46.8% reported by the European registry [34]. This finding was not surprising, since it reflects the trend in the general population. As in the general population, older patients seem at least partially to be protected by circulating antibodies from previous seasonal epidemics [35]. The reported A (H1N1) infection rate in CF patients was low, 2.2%. However, it is likely that these numbers underestimate the extent of A (H1N1) infection among patients with CF. It is possible that only the more severe cases visited the CF centres, and those that were mildly symptomatic were treated by community physicians. Furthermore, it is possible that some of the patients that live far from the centres preferred to be seen by local physicians; for those no data could be obtained. Only large epidemiological studies using serological tests would allow to determine spread of the A (H1N1) among patients with CF, by identifying also those without or with minor symptoms.

This study did not evaluate the actual vaccination coverage among CF patients in Europe. However, the finding that only 8.8% of the infected patients were vaccinated against A (H1N1) is disturbing. All the participating centres declared to have actively encouraged their patients to be vaccinated, and most

were successful. However, many centres reported that their patients had been infected before the vaccine was available. After introduction of the vaccination program only a few new cases with A (H1N1) infection were identified. Some of the participating centres reached high coverage, and others reported that after all their patients had been vaccinated no new case of A (H1N1) infection was identified. Earlier studies from the US and France reported influenza vaccination rates in the CF patient population of ≥75% [16,36]. This number, regarded as high, indicates that vaccination among patients with high-risk conditions such as CF is still suboptimal. The recent A (H1N1) vaccination coverage in the general population was low, despite a mass vaccination campaign to mitigate the transmission of the A (H1N1) 2009 pandemic-influenza [37]. This fact could affect the vaccination rate among patients with CF. We therefore speculate that earlier and wider coverage of the vaccine would have lowered the number of hospitalisations and the need for aggressive treatment, in agreement with the fact that influenza vaccination is recommended for all patients with CF.

In the present study, 80% of the patients received antiviral treatment with oseltamivir. It has been shown that early therapy with oseltamivir, when started during the first 48 hours of illness, shortened the duration of viral shedding [38]. In the current study we do not know if oseltamivir was started within 48 hours and if the severe cases deteriorated *despite* oseltamivir therapy. Although we did not intend to compare the adverse pulmonary effect of A (H1N1) with that of other viruses, this study demonstrates that a viral epidemic or pandemic such as A (H1N1) can have a significant impact on patients with CF. It is therefore essential to take serious measures for prevention and treatment of the disease. Rigorous implementation of hand washing and avoiding infection transmission through contact with infected individuals may decrease morbidity and severe complications in the CF population. In addition, vaccination of household members, healthcare workers and CF medical teams is also recommended to reduce the rate of infection among patients [39]. No clear data are available on the therapeutic value of preventive post-exposure use of antiviral drugs.

We are now in a post-peak period, with decreased pandemic activity. However, since it is uncertain if additional waves will occur, countries should be prepared for a second wave of infection. Despite previous reports, including only a small number of patients, showing that A (H1N1) infection caused mild disease [17,18], this report demonstrates that viral infection is associated with increased morbidity, and in certain patients with mortality. We therefore recommend that patients with CF, their families and their health care providers be aware of the risks of infection. Early and extensive introduction of a vaccination campaign should be considered, and methods to enhance infection control should be rigorously introduced in order to prevent infection of CF patients.

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