INFLUENZA A/H1N1 IN PATIENTS WITH CYSTIC FIBROSIS IN ITALY: A MULTICENTER SURVEY OF THE ITALIAN CF SOCIETY

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33rd Conference ECFS, Valencia, Spain
June 16-19, 2010

BACKGROUND

- Viral respiratory tract infections are well recognised precipitants of acute deterioration in patients with Cystic Fibrosis (CF)
- Observational studies have also suggested that viral respiratory tract infections may exhert a long-term adverse outcome in terms of lung function and disease progression
- Several mechanisms have been proposed to be responsible of these deleterious effects:
  → direct pathogenic effect of the viruses, that may be synergistic with bacteria in their capacity to damage the respiratory tract
  → distruction and desquamation of the airway epithelium by respiratory viruses, leading to reduced clearance of inhaled microrganisms and increased capacity for bacterial invasion.
- Viral respiratory tract infections may "pave the way" for colonisation and chronic infection with *P.*aeruginosa and other bacteria
- Thus the consequences of viral infections, including those caused by influenza viruses, are more severe in CF than in healthy individuals
- During 2009 a novel swine-origin pandemic influenza A virus, containing a combination of gene segments from North American and Eurasian lineages, was identified as the cause of outbreaks of febrile respiratory infection ranging from self-limited to severe illness
- Pandemic influenza A (H1N1) started in Italy at the beginning of September 2009 and patients with CF were included among those at risk who should receive A/H1N1 vaccination

AIM

To characterize the impact of 2009 pandemic influenza A (H1N1) in the Italian CF population

METHODS

- A multicenter case-control study was carried out within the Italian Cystic Fibrosis Society (SIFC) to collect clinical data of patients with confirmed A/H1N1 virus infection
- A questionnaire was sent to the 34 Italian CF Centers
- Enrolment of patients occurred according to the following inclusion criteria:
  - influenza-like illness suggestive symptoms
  - positivity for A/H1N1 virus at nasopharyngeal swab (RT-PCR)
- Inclusion criteria for enrolment of CF controls were:
  - influenza-like illness suggestive symptoms
  - negativity for A/H1N1 virus at nasopharyngeal swab (RT-PCR)
- The following clinical information for CF cases and CF controls were collected by participating Centers:
  - Gender, age, weight, height and BMI
  - Pancreatic status, sputum microbiology
  - Presence of comorbidity factors (e.g. diabetes, immunosuppression for organ transplantation)
  - Vaccination against influenza A/H1N1 (date)
  - Symptoms at onset of influenza
  - Antiviral therapy (duration and dose)
  - FEV1%: before, during and after (1 and 6 months) influenza A/H1N1
  - Complications, including pulmonary exacerbations, need for O2 therapy, etc.
  - Course of the disease over the 6 months following influenza A/H1N1

Statistical procedure

- Relative Risk (RR) and 95% CI of occurrence of symptoms and complications in CF Cases vs CF Controls were calculated.
- Differences in continuos variables between CF Cases and CF Controls were investigated by unpaired t-test.
- Binomial test was applied for dichotomic variable comparison.

RESULTS

- Overall 65 CF cases with confirmed A/H1N1 infection and 47 CF controls were reported from 17 Centers.
- 6 Centers did not enrol any patient because they did not observe any virologically confirmed influenza A /H1N1 infection among their patients
- 11 Centers did not replay to the questionnaire

Table 1. Demographic and clinical characteristics of CF patients enrolled

	CF CASES (n=65)	CF CONTROLS (n=47)	p-value
Gender (Males/Females)	38/27	24/23	NS
Age (mean, range) (years)	16.3 (0.5 –39)	19.3 (0.3 – 48)	NS
BMI (mean, range)	20.3 (13.8 – 27.5)	20.4 (16.1 – 26.1)	NS
BMI or W/L percentile (mean, range)	45.0 (2 – 98)	44.4 (1 – 98)	NS
FEV1% (mean)	61.9% (12 – 134)	61.2% (20 – 110)	NS
Pancreatic Insufficiency	58 (89.2%)	42 (89.3%)	NS
Pseudomonas aeruginosa	32 (49.2%)	24 (51.1%)	NS
Other Gram negative bacteria	2 (3.1%)	2 (4.3%)	
On O2 therapy	9 (13.8%)	6 (12.8%)	NS
Liver disease	14 (21.5%)	10 (21.2%)	NS
Portal hypertension	3 (4.6%)	0	
Diabetes	22 (33.8%)	9 (19.1%)	0.03
Organ transplantation	4 (6.2%) (1 liver; 3 lungs)	3 (6.3%) (3 lungs)	
Vaccination against A/H1N1 *	9 (13.9%)	7 (14.9%)	NS

* within 2 weeks on influenza onset

Table 2. Symptoms at onset

Symptom	CF CASES (n=65)	CF CONTROLS (n=47)	RR (95%CI)
Fever	60 (92.3%)	37 (78.7%)	1.19 (1.01 – 1.4)
Cough	29 (44.6%)	28 (59.5%)	0.77 (0.54 – 1.10)
Arthralgia	6 (9.2%)	4 (8.5%)	1.08 (0.32 – 3.63)
Headache	9 (13.8%)	3 (6.3%)	2.41 (0.70 – 8,28)
Dyspnoea	4 (6.1%)	10 (21.2%)	0.43 (0.17 – 1.11)
Hemoptysis	2 (3.07%)	2 (4.2%)	0.72 (0.11 – 4.95)

Antiviral therapy

- 53 of the 65 influenza A /H1N1 positive patients (81.5%) were treated with Oseltamivir at the dose of 131.4mg (range 24 – 150) for a mean period of 5.6 days (range 3 - 12)
- Only 5 of the 47 influenza A /H1N1 negative patients (10.6%) were treated with Oseltamivir at the dose of 120mg (range 90 – 150). All patients in control group were treated for 5 days

Duration of illness

- Patients with influenza A/H1N1 had a duration of the disease that was significant shorter than H1N1 negative CF Controls (7.4±7.1 days vs 11±4.7 days, p = 0.012).
- Influenza A/H1N1was uncomplicated in 22 cases (33.8%) as compared to 8 cases (17%) of influenza-like illness in CF controls.

Table 3. Clinical course of Influenza illness and complications in CF Cases and CF Controls

	CF CASES (n=65)	CF CONTROLS (n=47)	RR (95%CI)
Pulmonary exacerbation	43 (66.1%)	39 (82.9%)	0.80 (0.64 – 0.99)
Hospitalization	42 (64.6%)	34 (72.3%)	0.97 (0.76 – 1.23)
Oseltamivir treatment	53 (81.5%)	5 (10.6%)	6.85 (2.98 – 15.72)
Duration of Oseltamivir treatment (days)	5.6±1.6	5.0±0	p = 0.009
Atelectasia	0	1 (2.1%)	
Permanent need for O2 therapy	1 (1.5%)	0	1.09 (0.41 – 2.84)
Death	3 (4.6%)	1 (2.1%)	2.17 (0.23 – 20.2)

Table 4. Clinical characteristics of CF patients who died

	CF CASES (n = 3)	CF CONTROLS (n = 1)
Gender (M/F)	0/3	1/0
Age (yrs)	18 – 25 - 32	36
Vaccinated against influenza A/H1N1	0	0
Breathlessness at onset	2	1
Fever at onset	3	1
Antiviral therapy	3	0
Mean baseline FEV1 (% of predicted)	24 – 24 - 29	36
Sputum Microbiology	P.*aeruginosa* (1) B.*cepacia* (2)	P.*aeruginosa*
BMI (kg/m^2)	13.8 – 16 – 19.1	21.7

LONG TERM OUTCOME

- During the follow-up mean FEV1 did not change significantly in both groups (Table 5).
- At six months from the onset of influenza-like illness, a reduction of FEV1>10% was observed in 6/36 (16.7%) of A/H1N1 positive patients and in 9/22 (40.9%) of negative patients (RR 0.41, 95% CI 0.17 – 0.99).
- Over the same period, 39 of the 58 surviving A/H1N1 positive patients (67.2%) and 34 of the 45 surviving A/H1N1 negative patients (75.6%) had one or more pulmonary exacerbation(s) (RR 0.89, 95% CI 0.70 – 1.14)
- In both groups of patients there were no significant changes in sputum microbiology

Table 5. FEV1 in CF Cases and CF Controls before and 6 months after onset of Influenza A/H1N1 or Influenza-like illness*

TIME	CF CASES (n=36)	CF CONTROLS (n=22)	P
Before (mean±SD)	64.4±27.2	61.8±20.7	NS
After 6 months (mean±SD)	62.8±26.5	61.7±27.1	NS
p	NS	NS	NS

*data not yet available for 36 patients

CONCLUSIONS

- The number of CF patients with virologically confirmed Influenza A/H1N1 infection reported by Italian CF Centers during the pandemic period in Italy is limited (< 2% of Italian CF patients in regular follow-up)
- The disease was frequently complicated by acute pulmonary exacerbation often requiring hospitalisation, however at a rate that did not differ from CF A/H1N1 negative controls
- The clinical course and long-term outcome of influenza A/H1N1 may be quite severe, particularly in more compromised patients, but again at a rate not significantly different from CF controls
- Our data confirm the importance of vaccination against influenza viruses in CF