2009 H1N1 influenza A in cystic fibrosis patients. A French collaborative study

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Background: Influenza viruses have been shown to cause disease progression in Cystic Fibrosis (CF). The aim of this study was to document the influence of the pandemic H1N1 influenza A 2009 (H1N1/09) outbreak on the outcome of CF patients.

Methods: 12 French CF centers contributed retrospective and prospective data for patients with laboratory-confirmed H1N1/09 from 15 October 2009 to 15 December 2009.

Results: 47 symptomatic cases were reported. Mean age of the patients was 15 years (0–55 yrs). 38% had a chronic Pseudomonas aeruginosa sputum colonisation. Mean FEV1 (% predicted) was 82% (25–114%). Three patients had undergone lung transplantation. The most common symptoms were fever (100% of the patients), increased cough and sputum production (82%), asthma (58%), and worsening of dyspnea (47%). A large proportion of the patients (90%) received oseltamivir and 70% antibiotics. Twelve patients (25%) required hospitalization. The most common reason for admission was dyspnea and hypoxemia. Length of stay ranged from 2 days to 2 months. Three patients were admitted in intensive care unit. Two were put on lung transplant list because of severe respiratory failure, one of those being transplanted 1 month after influenza infection.

At follow up, 4 patients underwent colonization with *P. aeruginosa*. About 50% of the patients whose respiratory function tests were available, had a significant decrease in FEV1 in comparison to baseline [at 3 months: −12% (−9% to −29%) and at 6 months: −14% (−9% to −18%)].

Conclusions: This case series evidences the pronounced morbidity of H1N1/09 in worsening CF disease and predisposing to subsequent bacterial infections.

Identification of human coronaviruses among Brazilian children with cystic fibrosis

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Sino-nasal involvement in CF has been proposed as a gateway and reservoir for pulmonary infection with *P. aeruginosa*. Mucoid (M) and non-mucoid (NM) *P. aeruginosa* isolates from sinuses and lungs have been phenotypically and genotypically characterized in order to reveal adaptive mechanisms specific to the two compartments of the “united airways”.

Twenty-three *P. aeruginosa* isolates representing M and NM pairs from sinus and lung from 6 chronically infected CF patients were included in the study. The isolates were obtained by Functional Endoscopic Sinus Surgery and from sputum samples. Phenotypic and genotype characterizations as well as microarray analysis (Affymetrix) were performed.

Sino-pulmonary paired isolates belonged to the same clone, which has been isolated from the lung of the patients prior to sinus surgery. The same *mucA* and *lasR* mutations were identified in the sino-pulmonary pairs of M or NM isolates in all but one patient. No significant differences were found between the phenotypes and the overall gene expression profiles when all pairs were compared together. Analysis of gene expression data in individual patients showed that the numbers of differentially expressed genes between sinus and lung isolates varied from 0 to 65 for M and from 2 to 81 for the NM isolates.

Genes involved in response to oxidative stress and in amino acid metabolism were found to be differentially expressed between sinus and lung isolates of several patients suggesting differences in the inflammation and growth conditions between the two locations. Similar evolution of the bacteria in the two locations and/or bidirectional communication between sinus and lung is suggested.

Microevolution of the major common *Pseudomonas aeruginosa* clones C and PA14 in cystic fibrosis lungs

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*Pseudomonas aeruginosa* is an important causative agent of nosocomial infections and is the pathogen which contributes most to the shortened life expectancy in CF-patients. This study investigated the microevolution of the two major clonal complexes of the *P. aeruginosa* population, in serial cystic fibrosis (CF) airway isolates collected over 20 years since the onset of colonization. High-throughput sequencing-by-synthesis of the intermediate, late isolates and subsequent multimarker SNP genotyping of the whole strain panel revealed highly discordant temporal evolution of clones C and PA14 in the two patients. The PA14 lineage acquired about one mutation per year and diversified into just three branches. The Clone C lineage, however, acquired close to 1,000 SNPs within 23 years after hypermutable strains with a loss-of-function mutation in the *mutL* gene of the mismatch repair system (MMR) had emerged. Competitive growth experiments of the first and late C or PA14 CF isolates suggested that neither a large deletion nor the acquisition of non-neutral amino acid substitutions in 10% of the proteome during CF lung colonization had compromised global fitness. In contrast to expectation no preference to targets that trigger the known phenotypic conversion was noted. The clone C lineage had accumulated numerous mutations in core genes involved in metabolism and gene expression. Targets that are commonly associated with the phenotypic signature of *P. aeruginosa* in CF lungs were not overrepresented. These findings implicate that not only virulence factors are affected during CF infection but metabolism and gene expression play a more important role than appreciated.