Cystic Fibrosis and Atopy

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Cystic fibrosis (CF) is the most common autosomal recessive disorder in Caucasians (1:2500 to 1:10000 live newborns). The genetic defect of CF results from abnormalities of chromosome 7 that causes dysfunction in cystic fibrosis transmembrane conductance regulator (*CFTR*), a protein that regulates chlorine ion transport. It results in mucus thickness and reduction of mucociliary clearance, predisposing the patient to inflammation and colonization by *Staphylococcus aureus and Pseudomonas aeruginosa*. Genetic and environmental factors may influence the clinical phenotype of CF. The coexistence of allergy could affect the clinical phenotype of CF . Rhinosinusitis is frequent in CF and causes serious anatomic alterations in the sinus, although few patients spontaneously report symptoms, often underestimated in comparison with severity of the pulmonary disease. [1]

Cystic fibrosis and asthma are not always easily distinguished from each other.[2]
Wheeze, whether in asthmatic or CF patients, is a result of airway obstruction due to inflammation, bronchospasm and retained secretions. Both diseases may coexist in the same patient, and poor lung function and bronchial hyperresponsiveness are common to both.[3]
Bronchodilator response may be found in CF and demonstrates that this medication may help alleviate the airflow limitation. Eosinophilia and high serum IgE leves are of limited value but personal and family history of atopy may be helpful. [4,5] In earlier study 47% of cystic fibrosis heterozygotes had positive prick skin tests to 1 or more antigens and 53% had histories of allergic disease, both occurring significantly more often than in a control group. [6]

A cross-sectional study of 55 CF adult patients with upper and lower airway disease demonstrated that allergen specific IgE was present to at least 1 aeroallergen in 67% by skin prick testing and 80% by RAST. Rhinitis occurred in 50% of the population with no detectable difference in lung function between those with and without allergic sensitization. The authors concluded that individuals with CF should be evaluated for coexistent allergy and this warrants appropriate therapy. The rate of allergy to *Aspergillus* in this study was much lower than that reported in studies of children and adolescents with CF. These differences could be explained by the methods of detecting *Aspergillus* specific IgE, potency of allergenic extracts, degree of environmental exposure *to Aspergillus* , prevalence of allergic disease and IgE sensitization to molds in general population.[7]

The frequent evidence of allergy could be explained by abnormalities in epithelial barrier function and mucus hypersecretion leading to retention of allergens in the respiratory tract with progressive exposure and sensitization. Alternatively, a genetic predisposition to allergy has been suggested by studies of individuals heterozygous for CF. Mutations in the gene responsible for CF may be associated with the development of chronic rhinosinusitis (CRS) in the general population. One hundred forty-seven patients who met stringent diagnostic criteria for CRS were compared with 123 CRS-free controls. Eleven CRS patients were found to have a CF mutation (ΔF508, n = 9; G542X, n = 1; and N1303K, n = 1). Diagnostic testing excluded CF in 10 of these patients and led to CF diagnosis in 1. Excluding this patient from the analyses, the proportion of CRS patients who were found to have a CF mutation (7%) was significantly higher than in the control group (n = 2; P =.04, both having ΔF508 mutations). Furthermore, 9 of the 10 CF carriers had the polymorphism M470V, and M470V homozygotes were overrepresented in the remaining 136 CRS patients (P =.03).[8]

Sinus disease in CF presents several clinical, endoscopic and tomographic affections. Even though most of them are not correlated with severity and disease genotype, the presence of polyposis could be genotype-dependent and that patients' age is associated with severity of CF.
The prevalence of nasal polyposis varies from 7% to 56% and it is greater among homozygote for DF 508. There is no association between affections in paranasal sinus CT scan and severity of cystic fibrosis (CF).[9]

CF patients identified at neonatal screening and having diagnosis confirmed by sweat test or CF mutations are referred to CF clinic at University of Parana General Hospital. Currently 97 patients are followed in this multi-professional clinic and have led to several clinical reports and research protocols in allergy-immunology, nutrition, genetic, and microbiology areas. In one of these studies 47 CF patients (mean age 12,4 ± 5,2years) were examined for nasosinusal symptoms, allergy prick skin test responses, paranasal sinuses CT scans and nasal fibroscopy; 38% were asymptomatic, and sneezes and nasal pruritus were most common nasal symptoms respectively in 57% and 43%. Nasal polyps were seen by

endoscopy in 23% of the cases, with predominance in the medium meatus (89%). Most patients had CT abnormalities: absence of aeration (91,5%), disease of the anterior ethmoid-maxillary complex (87,2%) and of the sphenoid sinus (42,6%), aplasia of frontal sinus (68,1%) and bulging of the nasal lateral walls (48,9%) were the most common findings. SPT response to at least one inhalant allergen was observed in 49% of patients: *D. pteronyssinus* 33%, *Blomia tropicalis* 21%, cockroach 8%, *Aspergillus* 7%, cat epithelia 5,4% and dog 5%. We conclude that nasal endoscopy is essential in the diagnosis of nasal polyposis, paranasal CT scans are abnormal in most CF patients (pansinusitis with frontal aplasia and bulging of medial maxillary sinus wall is pathognomic of CF) even though nasal symptoms are not those of chronic rhinosinusitis. IgE sensitization to inhalant allergens may be more frequent in CF patients than in general population. [10]

From March to September 2011, another sample of 40 CF patients (median age 7.3 years) were screened for allergic bronchopulmonary aspergillosis by means of SPT response to aeroallergens, eosinophil counts, sputum culture,serum total IgE and specific IgE to *Aspergillus fumigatus* (ImmunoCAP). SPT response was positive in 50% of patients and 30% was positive to *D.pteronyssinus.* However a positive response to *Aspergillus fumigatus* was observed in 9/40 (23%) and serum specific IgE ≥ 0.35 kU/L in 10 patients. There was good correlation between SPT and specific IgE ($p<0.0001$) . Rhinitis was found in 22 (55%) and only 2 patients had sputum culture positive for *Aspergillus sp* despite negative SPT/IgE to the fungus. Three patients had diagnosis of ABPA (CF Foundation Criteria[11]) with radiological abnormalities (infiltrates and/or bronchiectasis), 2 had serologic ABPA and the remaining 4 had only sensitization to *Aspergillus.* Patiens with CF should be periodically screened for ABPA and sensitized patients should be closely monitored. Clinical deterioration, elevated total IgE and specific IgE to *Aspergillus* are minimal criteria for ABPA and may indicate treatment for ABPA(unpublished observation).

Special attention should be given to *A. fumigatus,* the most prevalent mould allergen identified in CF patients. When considering CF and ABPA, although sensitization to *A. fumigatus* is crucial to ABPA diagnosis ,it is important to differentiate lung colonization by *Aspergillus*, allergic sensitization , and clinically proven ABPA , a sizeable minority ranging from1% to11%. The progression from simple sensitization to ABPA constitutes a crucial phase that urges to be correctly diagnosed in order to prevent the establishment of disease.[3] *Aspergillus* sensitization is associated with reduced lung function in asthma and CF, and may be associated with reduced survival in children with CF. [12-14]
CF patients with *A. fumigatus* sensitization and ‘‘true’’ ABPA differ in terms of specific IgE responses to recombinant allergens (rAsp f 1, rAsp f 2, rAsp f 3, rAsp f 4 and rAsp f 6). [15,16]

Asthmatic patients sensitized to *A. fumigatus* react with 100% specificity and 88% sensitivity to rAsp f 1 and rAsp f 3. On the other hand, patients with ABPA present almost exclusively specific IgE to rAsp f 4 and rAsp f 6, suggesting that specific IgE to recombinant allergens of *A. fumigatus* could help in early detection of sensitization and ABPA itself, with proven superiority to allergen extracts. [3]

Allergic inflammation in CF may contribute to nasal disease and lower airways, poorer lung function in association with *Aspergillus* sensitization. Immunoallergic evaluation is important for a correct approach of these patients. [17]

The link between *CFTR* mutations in ABPA was investigated in a systematic review of four studies (79 ABPA, 268 controls). The odds of encountering *CFTR* mutation was higher in ABPA compared with the control group (OR 10.39; 95% CI, 4.35-24.79) or the asthma population (OR 5.53; 95% CI 1.62-18.82). [18]

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