

this group. Although rare, anaphylactic reactions to PPIs have been described.<sup>1-7</sup>

They have modified benzimidazoles with a pyridine ring and chemically related structures. A number of case reports suggesting cross-reactivity patterns among lansoprazole and rabeprazole,<sup>2,3</sup> omeprazole and lansoprazole,<sup>4-6</sup> and omeprazole and pantoprazole<sup>1,4</sup> have been reported. Our patient had IgE-mediated anaphylactic or urticarial reactions to lansoprazole, which were confirmed by her history and positive SPT results. However, SPT and IDT were negative for other PPIs including, omeprazole, pantoprazole, esomeprazole and rabeprazole. In addition, the oral challenge test showed that our patient tolerated therapeutic doses of omeprazole, pantoprazole, esomeprazole and rabeprazole. Vovolis reported IgE mediated allergic reaction to rabeprazole with good tolerance to omeprazole and lansoprazole.<sup>7</sup> To the best of our knowledge, our patient is the first reported case of anaphylaxis induced by lansoprazole with good tolerance to other PPIs including rabeprazole.

In conclusion, cross-reactivity between PPIs is conflicting. We also showed that controlled oral challenge test using PPIs for which the SPT is negative is a safe approach to choose an alternative drug.

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## Cystic fibrosis and atopy

To the Editor,

Cystic fibrosis (CF) is the most common autosomal recessive disorder in Caucasians (1:2500-1:10,000 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 colonisation by *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Coexistence of allergy, as well as genetic and environmental factors may influence the 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 the severity of the pulmonary disease.<sup>1</sup>

Cystic fibrosis and asthma are not always easily distinguished from each other.<sup>2</sup>

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 hyper-responsiveness are common to both.<sup>3</sup>

Bronchodilator response may be found in CF and demonstrates that this medication may help to alleviate the airflow limitation. Eosinophilia and high serum IgE levels are of

limited value but personal and family history of atopy may be helpful.<sup>3</sup>

Since 1 in 20 of the population are CF mutation carriers and have CFTR protein dysfunction, this would contribute to allergy in the community. In earlier study 47% of cystic fibrosis heterozygotes had positive prick skin tests to one or more antigens and 53% had histories of allergic disease, both occurring significantly more frequent than in a control group.<sup>4</sup>

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 one 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 sensitisation. 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 sensitisation to moulds in general population.<sup>5</sup>

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 sensitisation. 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 and forty-seven patients who met stringent diagnostic criteria for CRS were compared with 123 CRS-free controls. Eleven CRS patients were found to have one CF mutation ( $\Delta F508$ ,  $n=9$ ;  $G542X$ ,  $n=1$ ; and  $N1303K$ ,  $n=1$ ). Diagnostic testing excluded CF in 10 of these patients and led to CF diagnosis in one. 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  $\Delta F508$  mutations). Furthermore, 9 of the 10 CF carriers had the polymorphism  $M470V$ , and  $M470V$  homozygotes were over-represented in the remaining 136 CRS patients ( $P=.03$ ).<sup>6</sup>

Sinus disease in CF presents several clinical, endoscopic and tomographic findings. 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  $DF508$ . There is no association between affections in paranasal sinus CT scan and severity of cystic fibrosis (CF).<sup>7</sup>

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  $12.4 \pm 5.2$  years) were examined for nasosinus symptoms, allergy prick skin test responses, paranasal sinuses CT scans and nasal fibroscopy; 38% were asymptomatic, and sneezes and nasal pruritus were the most common nasal symptoms respectively in 57% and 43% of the cases. Nasal polyps were identified by endoscopy in 23% of the cases, with predominance in the middle 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)<sup>8</sup> even though nasal symptoms are not those of chronic rhinosinusitis. IgE sensitisation to inhalant allergens may be more frequent in CF patients than in the general population.<sup>9</sup>

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, specific IgE to *Aspergillus fumigatus* (ImmunoCAP) and precipitins to *Aspergillus* by radial immunodiffusion. SPT response was positive in 50% of patients and 30% were positive to *D. pteronyssinus*. However, a positive response to *Aspergillus fumigatus* was observed in 9/40 (23%) and

serum specific IgE  $\geq 0.35$  kU/L in 10 patients. The data about precipitins is not shown due to inconsistent results. There was good correlation between SPT and specific IgE ( $P<0.0001$ ). Rhinitis was found in 22 (55%) and only two patients had sputum culture positive for *Aspergillus* sp. despite negative SPT/IgE to the fungus antigen. Three patients had diagnosis of ABPA (CF Foundation Criteria) with radiological abnormalities (infiltrates and/or bronchiectasis), two had serologic ABPA and the remaining four had only sensitisation to *Aspergillus*. Patients with CF should be periodically screened for ABPA and sensitised 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 sensitisation to *A. fumigatus* is crucial to ABPA diagnosis, it is important to differentiate lung colonisation by *Aspergillus*, allergic sensitisation, and clinically proven ABPA, a sizeable minority ranging from 1% to 11%. The progression from simple sensitisation to ABPA constitutes a crucial phase that urges to be correctly diagnosed in order to prevent the establishment of disease.<sup>3</sup> *Aspergillus* sensitisation is associated with reduced lung function in asthma and CF, and may be associated with reduced survival in children with CF.<sup>10</sup>

Asthmatic patients sensitised to *A. fumigatus* react with 100% specificity and 88% sensitivity to rAspf1 and rAspf3. On the other hand, patients with ABPA present almost exclusively specific IgE to rAspf4 and rAspf6, suggesting that specific IgE to recombinant allergens of *A. fumigatus* could help in early detection of sensitisation and ABPA itself, with proven superiority to allergen extracts.<sup>3</sup>

Allergic inflammation in CF may contribute to nasal disease and lower airways, poorer lung function in association with *Aspergillus* sensitisation. Immunoallergic evaluation is important for a correct approach of these patients.<sup>11</sup>

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 were 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).<sup>11</sup>

Changes of the *CFTR* protein determine the different phenotypes of CF through a not well known mechanism but certain conditions such as chronic rhinosinusitis, ABPA, asthma and bronchiectasis, have been linked to the *CFTR* gene. CF phenotypes may result from two or a single *CFTR* mutation in combination with modifier genes and environmental factors. Understanding the genetic basis of CF in addition to the current knowledge of airway surface liquid may positively influence disease management and outcomes.

## Ethical disclosures

**Patients' data protection.** Confidentiality of Data. The authors declare that they have followed the protocols of their work centre on the publication of patient data and that all the patients included in the study have received

sufficient information and have given their informed consent in writing to participate in that study.

**Right to privacy and informed consent.** Right to privacy and informed consent. The authors have obtained the informed consent of the patients and/or subjects mentioned in the article. The author for correspondence is in possession of this document.

**Protection of human subjects and animals in research.** Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the responsible Clinical Research Ethics Committee and in accordance with those of the World Medical Association and the Helsinki Declaration.

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