Increased frequency of asymptomatic bronchial hyperresponsiveness in nonasthmatic patients with food allergy

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ABSTRACT: Subclinical inflammation in gut mucosa has been demonstrated in bronchial asthma suggesting the whole mucosal system is involved in allergic diseases. The presence of subclinical bronchial involvement was assessed by nonspecific bronchial hyperresponsiveness (BHR) in nonasthmatic patients with food allergy (FA).

BHR was studied in 35 patients with various manifestations of FA without food-induced asthma. Sixteen had a previous history of asthma and/or rhinitis to aeroallergens (group A), whereas 19 patients (group B) did not. BHR was defined by a provocative dose causing a 20% fall in forced expiratory volume in one second of (PC₂₀) <8 mg·mL⁻¹ of methacholine.

Asymptomatic BHR occurred frequently in nonasthmatic patients with FA (10 of 19, 53%); this did not significantly differ from patients with FA and a previous history of asthma and/or rhinitis to aeroallergens (13 of 16, 81%). PC₂₀ was significantly lower in group A (1.84±0.53 mg·mL⁻¹) than in group B (3.35±0.74 mg·mL⁻¹; p<0.05). The number of patients with positive skin tests to aeroallergens was similar between groups. Sequential evaluation, performed 1 year after initial evaluation, in 7 nonasthmatic patients (group B) demonstrated a similar level of BHR.

The present study demonstrated that BHR is a frequent finding in nonasthmatic patients with food allergy which may be due, at least in part, to a subclinical inflammatory process in the bronchi.

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Subclinical inflammatory changes in gut mucosa have been recently demonstrated in patients with asthma, suggesting that a diffuse involvement of the mucosal immune system occurs as a cause or as a consequence in asthma [1]. Conversely several clinical studies demonstrated that inflammatory diseases of gut mucosa, were associated with subclinical involvement of bronchial mucosa [2–4]. For example, an increased frequency of asymptomatic bronchial hyperresponsiveness (BHR) was reported in nonasthmatic patients with inflammatory bowel disease. This finding suggests that the inflammatory bowel disease alone favours the development of nonspecific BHR, probably through the activation of the common mucosal immune system [4].

The authors took this into consideration and hypothesized that subclinical BHR may be present in nonasthmatic patients with food allergy (FA). To demonstrate this, they investigated the presence of nonspecific BHR using an inhaled methacholine provocation test in 35 consecutive patients with various manifestations of FA, excluding food-induced asthma.

Patients and methods

Patients and procedure

Thirty-five nonsmoking patients with FA but without food-induced asthma or rhinitis (19 females and 16 males; mean age 34±3 yrs), were included in the study.

The diagnosis of FA was established using clinical criteria and selected laboratory procedures [5] including: 1) historical documentation of reactions to specific foods; 2) positive skin-prick tests to a specific food allergen and the serum specific immunoglobulin-E (IgE) antibodies directed against the food allergen, measured by the Phadebas radioallergosorbent test (RAST, Pharmacia diagnostic, Upsalla, Sweden); 3) resolution of symptoms under a strict food allergen free diet to observe whether the reported symptoms will be resolved by the removal of one or more foods from the diet; 4) rapid and reproducible clinical symptoms after a single-blind placebo-controlled challenge; and 5) correlation between the positive food allergen ingestion challenge and the results of skin tests and the serum specific IgE antibodies directed against the food allergen. All patients exhibited type 1 hypersensitivity symptoms which occurred minutes or a few hours after ingestion of the food allergen (table 1). The single-blind placebo-controlled challenge was not performed in patients who reported anaphylactic reactions. In these patients, the diagnosis of FA relied on criteria 1–3 only. The single-blind placebo-controlled challenge, with the native food mixed with apple compote, induced the reproducible clinical symptoms within a few minutes. Examination of stools and systematic serological tests, against the standard parasitic diseases, were performed in order to discard the possibility of a parasitic involvement at the small intestine level. A food allergen elimination diet was given after diagnosis, which resulted

Table 1. – Clinical characteristics of the 35 patients with food allergy

	Group A	Group B
Subjects n	16	19
Age yrs	34±4	34±3
Urticaria	12	14
Angioedema	13	15
Anaphylactic shock	4	6
Digestive symptoms	2	6
Positive skin tests to aeroallergens	12	8
House dust mite	10*	5
Animal danders	0	0
Pollens	8	7
Moulds	0	0
Eosinophils cells·mm ⁻³	258±36	453±171
Total IgE kU·L ⁻¹	444±144	433±177
Food hypersensitivity		
Drupaceous/umbelliferous [#]	5	9
Exotic fruits ⁺	6	9
Solanaceous [‡]	3	7
Peanut	4	3
Crustaceans	6	2

Results are presented as mean±SEM. *: significantly different from group B, $p<0.05$; #: group includes, peach, strawberry, carrot, celery; +: group includes, kiwi, banana, avocado; ‡: group includes, tomato, sweet pepper. Group A: patients with a previous history of asthma and/or rhinitis; Group B: patients without a history of asthma and/or rhinitis; IgE: immunoglobulin E.

in resolution of the symptoms for all patients. All the patients were untreated at the time of the study.

Respiratory evaluation included skin-prick tests to aeroallergens, spirometric measurements and methacholine challenge. Respiratory evaluation was performed at least 2 months after diagnosis of FA and the last manifestations of FA. Skin-prick test to aeroallergens (house dust mite, animal danders, pollens, moulds) were performed in all cases. Asthma was defined according to the criteria suggested by the American Thoracic Society (ATS) [6]. Exclusion criteria for patients with a previous history of asthma were a forced expiratory volume in one second (FEV₁) <70% predicted (pred) value, lower respiratory tract infection in the previous 8 weeks, asthmatic exacerbation in the preceding 8 weeks and treatment with inhaled or oral corticosteroids in the 4 months before the study. Rhinitis was defined as a characteristic history of perennial or seasonal nasal symptoms (sneezing, rhinorrhoea, obstruction, anosmia and itching). Overall, 16 patients (group A) had a previous history of asthmatic reactions and/or rhinitis due to hypersensitivity to aeroallergens and 19 patients did not exhibit any symptoms (group B).

Methods

Skin-prick tests. Skin-prick tests were performed as recommended [7]. Positive controls were histamine (10 mg·mL⁻¹) and codeine phosphate. The negative control solution was the diluent used to preserve the allergen extracts. Wheal diameters with these preparations ranged 3–7 mm. Skin tests were read at the peak of their reaction by measuring the wheal and the flare 15 min after the performance of the tests. Skin tests giving a wheal

diameter >3 mm when compared with the negative control were considered to be positive.

Food challenge. Food challenge was performed using apple compote as the vehicle. The vehicle itself was used as a placebo and the patients were given a volume that was approximately the same as that containing the challenge. The β -agonists, theophylline and cromolyn were avoided for 48 h prior to the challenge. An initial dose of 10–500 mg of dried food was administered in the vehicle. Increments progressed by doubling for several steps. Sequential evaluation of pulmonary function was performed during the food challenge (every 15 min during the first hour and then every hour) and no significant changes in FEV₁ were demonstrated. If no reaction was seen during the observation period, the challenge was judged as being negative [8, 9].

Pulmonary function tests and methacholine challenge. All measurements were made in the sitting position. FEV₁, forced vital capacity (FVC) and maximal forced mid-expiratory flow (FEF_{25%–75%}) were obtained from flow/volume curves using a spirometer (Medgraphics, St Paul, MN, USA). The largest values obtained for FVC, FEV₁ and FEF_{25%–75%} from the first three technically satisfactory forced expirations were selected. All data were expressed in absolute values and in per cent of predicted normal values (% pred) [10].

Methacholine challenge was performed sequentially with a DeVilbiss 646 nebulizer (output of 0.13 mL·min⁻¹) [10]. Patients inhaled the diluent solution for 2 min of tidal breathing followed by doubling concentrations of methacholine at intervals of 5 min, ranging 0.125–8 mg·mL⁻¹. The end-point for the procedure was a 20% fall in FEV₁ from post diluent values or when a methacholine concentration of 8 mg·mL⁻¹ was obtained. The lowest, technically satisfactory FEV₁ value obtained between 90 s and 3 min was used in the analysis to calculate the dose-response curve. Dose-response curves were constructed by plotting FEV₁ against increasing concentration of methacholine as a log scale. The provocative concentration (PC₂₀) was defined as the methacholine concentration necessary to decrease FEV₁ by 20% from baseline values. BHR was defined by a PC₂₀ <8 mg·mL⁻¹. Asymptomatic BHR was defined as a methacholine PC₂₀ <8 mg·mL⁻¹, in the absence of symptoms suggestive of asthma (intermittent wheeze, chest tightness, dyspnoea, recurrent cough), in subjects who reported never being told by a physician that they had asthma or that they required any asthma medication.

Statistical analysis

Group data are expressed as mean±standard error (SEM). Statistical analysis was performed using the Mann-Whitney U-test for quantitative data. Differences in qualitative data among the groups were examined by Fisher's exact test. Differences between paired data were investigated using the Wilcoxon's signed-rank test. A p -value <0.05 was considered to be statistically significant.

Results

The clinical characteristics of the group A (previous history of asthma or rhinitis) and group B patients (without

previous history of asthma or rhinitis) are reported in table 1. There was no significant difference for age, clinical manifestations of FA, prevalence of positive skin tests to aeroallergens and IgE levels between the two groups. Blood eosinophil count tended to be higher in group B than in group A.

There was no significant difference in baseline FEV₁ (mL) between the two groups although there was a trend toward a lower FEV₁ (%) in group A (table 2). The prevalence of BHR did not significantly differ in the two groups. Thirteen of 16 patients in group A (81%) and ten of 19 in group B (53%) exhibited nonspecific BHR. Methacholine sensitivity was higher in group A than in group B. Mean PC₂₀ was significantly lower in group A (1.84 ± 0.53 mg·mL⁻¹ methacholine) than in group B (3.35 ± 0.74 ; $p < 0.05$). In addition, FEV₁ decrease was higher in group A than in group B at 0.125 mg·mL⁻¹ and at 0.5 mg·mL⁻¹ of methacholine concentrations (table 1, $p < 0.05$). Clinical and functional characteristics of the patients did not differ according to the presence of BHR.

Clinical and functional characteristics were similar in patients with or without positive skin tests to aeroallergens. The prevalence of nonspecific BHR was not statistically different between patients with positive skin tests to allergens (13 of 20) (65%) and patients with negative skin tests to aeroallergens (10 of 15) (66.6%). In addition, mean PC₂₀ was similar in these 2 groups (2.6 ± 0.6 mg·mL⁻¹ methacholine and 2.3 ± 0.7 mg·mL⁻¹ methacholine, respectively). Among the group B patients, the prevalence of positive skin tests to aeroallergens was similar in patients with BHR (4 of 10) and in patients without BHR (4 of 9).

Sequential evaluation was performed 1 yr after initial evaluation in seven patients from group B (three patients with positive skin tests to aeroallergens). These patients remained free of respiratory symptoms and did not exhibit any symptoms of FA between the two evaluations. PC₂₀ remained stable between the two evaluations (3.15 ± 0.7 mg·mL⁻¹ at the first evaluation, 2.9 ± 0.6 mg·mL⁻¹ at the second evaluation).

Table 2. – Functional characteristics of the 35 patients with food allergy

	Group A	Group B
Subjects n	16	19
FEV ₁ mL	3176±214	3055±158
FEV ₁ %	95.2±3	101.1±2.4
FVC mL	3832±228	3617±186
FVC %	100.6±2.8	102±2.8
FEV ₁ /FVC %	83.2±1.7	86.4±1.4
Normal response to methacholine	3	9
BHR	13	10
PC ₂₀ mg·mL ⁻¹	$1.84 \pm 0.53^*$	3.35 ± 0.74
Fall in FEV ₁		
0.125 mg·mL ⁻¹ *	$5.44 \pm 1.43^*$	1.21 ± 0.41
0.5 mg·mL ⁻¹ *	$12.1 \pm 3.33^*$	3.39 ± 1.12

Results are presented as mean±SEM. *: expressed as the percentage of forced expiratory volume in one second (FEV₁) decrease after the indicated concentration of methacholine. FVC: forced vital capacity; BHR: bronchial hyperresponsiveness; PC₂₀: provocative methacholine concentration causing a 20% fall in FEV₁; Group A: patients with previous history of asthma and/or rhinitis; Group B: patients without history of asthma and/or rhinitis.

Discussion

The present study clearly demonstrated an increased prevalence of asymptomatic BHR in nonasthmatic patients with FA (53%), which appeared to be similar to that observed in patients with FA and a previous history of asthma or allergic rhinitis (81%). In addition, it was found that asymptomatic BHR persisted over one year in nonasthmatic patients with FA, despite food allergen avoidance over the same period. To the best of the authors knowledge, this is the first demonstration of an increased prevalence of asymptomatic BHR in nonasthmatic patients with FA.

Since the reported prevalence of nonspecific BHR in the general population is low, the findings suggest that FA favours, by itself, the development of nonspecific BHR. The prevalence of nonspecific BHR in healthy subjects has been investigated in several studies [11–14]. The results of these studies have demonstrated that the prevalence of BHR in healthy adult subjects was low and increased with the degree of atopy. The prevalence of BHR, as defined by a histamine PC₂₀ <8 mg·mL⁻¹, was reported in a random population of 400 subjects by COCKROFT *et al.* [13]. The author found that the incidence of BHR was 5.9% in nonatopic nonasthmatic subjects and 9.2% in atopic nonasthmatic subjects. MALO *et al.* [14] also reported a low level (8%) of nonspecific BHR, as defined by a methacholine PC₂₀ <16 mg·mL⁻¹, in 100 healthy subjects. The role of sensitization to aeroallergens, in the development of asymptomatic BHR associated with FA, was examined since previous studies have identified atopy as a risk factor for the development of asymptomatic BHR. The authors found a higher frequency of sensitization to house dust mites in group A than in group B. This finding reflects the fact that dust mites are frequently the cause of asthma or allergic rhinitis. However, the prevalence of nonspecific BHR was similar whether sensitization to aeroallergens existed or not. Furthermore, the prevalence of asymptomatic BHR (group B patients) was similar in patients with positive skin tests to aeroallergens and in patients with negative skin tests to aeroallergens, suggesting that sensitization to aeroallergens is not the sole factor that determines the development of BHR associated with FA.

In FA, the sensitization to allergens occurs at the intestinal level but the clinical manifestations of FA are polymorphic. FA as the cause of asthma or increased nonspecific BHR in asthmatics appears to be infrequent (2–8.5%) [15–19]. Respiratory symptoms induced by food allergens, such as asthmatic symptoms, are rare. However, previous studies suggest that food-induced allergic reactions may increase airway reactivity in asthmatic patients with moderate-to-severe food-induced asthma [16–19]. In this study, the authors focused on the assessment of nonspecific BHR in nonasthmatic patients with FA after allergen avoidance, in order to investigate the presence of a subclinical bronchial involvement in FA. The fact that nonspecific BHR persisted over 1 yr after allergen avoidance suggests that nonspecific BHR in FA is not due to chronic allergen intake. This finding is in line with a previous report in which inflammatory changes of gut mucosa persisted several months after the last reported symptoms of FA [20].

An increased frequency of asymptomatic BHR was previously reported in several diseases of the mucosal immune system: allergic rhinitis, nonallergic rhinitis with eosinophilic syndrome, nasal polyposis and Crohn's disease [4, 21–23]. In these diseases, the presence of asymptomatic BHR was closely associated with bronchial inflammatory cellular changes, suggesting the involvement of the common mucosal immune system. It can be hypothesized that asymptomatic BHR in FA occurs through the recirculation of immune cells, namely T-lymphocytes, via the common mucosal immune system from the intestinal to the bronchial mucosa. Previous studies have examined the interaction between bronchial and intestinal mucosae in humans. The authors previously demonstrated that the intestinal permeability to chromium-51 labelled ethylenediamine tetraacetic acid (CrEDTA) was significantly higher in patients with asthma than in patients with chronic obstructive pulmonary disease or controls [24]. In addition, the intestinal mucosa in asthmatic patients exhibited "airway-like" pathological abnormalities, including a significant accumulation of mononuclear cells, of eosinophils and of inflammatory cells expressing interleukins 3 and 5 and granulocyte-macrophage colony stimulating factor in the lamina propria [1]. These asymptomatic pathological abnormalities of gut mucosa in asthma, were similar to those observed in the bronchial mucosa, supporting the hypothesis that the whole common mucosal immune system is involved as a cause or as a consequence in asthma.

The findings of the present study, which demonstrated an increased prevalence of nonspecific bronchial hyperresponsiveness suggest that subclinical abnormalities of the bronchial mucosa may occur in patients with food allergy. The significance of nonspecific bronchial hyperresponsiveness in food allergy is unclear; whether it predisposes to asthma, or is the expression of the activation of the bronchial mucosal immune system in patients, remains to be determined.

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