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The functional connection between oral allergy syndrome and united airways disease assessed by oral challenge

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ABSTRACT

Background: The airways and the upper digestive tract have a common embryonic origin. In sensitized subjects they can respond to allergens with an immediate reaction (asthma, rhinitis, or oral allergy syndrome [OAS]).

Objective: To investigate the possible functional connection between respiratory and upper digestive tract by means of specific oral allergen challenges.

Methods: Patients sensitized to birch and apple were subdivided into group A ($n = 12$; asthma + rhinitis caused by birch and OAS caused by apple); group B ($n = 10$; OAS caused by apple without asthma/rhinitis); group C ($n = 8$; asthma and rhinitis caused by birch without OAS). Healthy subjects represented the control group D ($n = 6$). Oral provocation test with apple was performed out of the pollen season. Visual analog scale for eye, nose, and mouth symptoms, spirometry, nasal eosinophil count, and exhaled nitric oxide were assessed before and 6 hours after challenge.

Results: No change occurred in nasal and ocular symptoms before versus after challenge in all groups. On the contrary, in groups A and B the oral scores significantly increased after challenge ($P < .001$), whereas no change was seen in groups C and D. Exhaled nitric oxide and nasal eosinophils showed no change before versus after challenge in all groups. Nitric oxide was higher before and after challenge in groups A and C vs groups B and D. No change was seen in either forced vital capacity or forced expiratory volume in 1 second.

Conclusion: In the case of birch-apple syndrome, eating apple does not functionally or clinically affect the respiratory tract.

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Introduction

The term “United Airways Disease” or “allergic rhinobronchitis” indicates the functional and immunological link between the nose and the bronchi in respiratory allergy.¹ In other words, the upper and the lower airways are considered as a single functional entity that responds to the offending allergen with the same inflammatory processes.² The concept of united airways is supported by numerous epidemiological surveys showing the frequent coexistence of allergic rhinitis (AR) and allergic asthma (AA) (for review, see Cruz et al³) and by mechanistic studies, showing that when 1 of the 2 districts is stimulated with an allergen, changes in the other district also occur.^{4,5} Whether a functional connection exists among upper and lower airways and upper digestive tract is unclear. This is of relevance because the upper airways and the upper digestive tract have a common early embryonic origin,⁶ and the upper digestive tract (the mouth in particular) of sensitized sub-

jects can respond to allergens with an immediate reaction that is well known as oral allergy syndrome (OAS).⁷ Oral allergy syndrome can be associated with respiratory allergies, as typically happens in the case of birch-apple syndrome, which is sustained by cross-reacting proteins or pan-allergens that are present in pollens and fruits.^{8,9} The aim of the present study was to investigate the possible functional connection between respiratory tract and upper digestive tract by means of specific allergen challenges in patients with united airways disease or OAS or both.

Methods

Patients sensitized to birch and apple with OAS, AA, or AR, variously combined, were enrolled for the study and underwent an open food challenge out of the pollen season, when they were symptom free. Before and after the oral challenge, several clinical and laboratory parameters were assessed. The study was approved by the inner ethical committee, and all patients signed an informed consent.

Patients and Diagnosis

Patients suffering from OAS or birch allergy were enrolled and subdivided into 3 groups according to their clinical characteristics.

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Table 1
Demographic Characteristics of the 4 Groups of Patients

	Group A OAS+ AR+ A+	Group B OAS+ AR- A-	Group C OAS- AR+ A+	Group D OAS- AR- A-
N. of patients	12	10	8	6
Mean age	39	40	38	41
Age range	29–51	31–50	30–52	29–48
Female/male	8/4	6/4	6/2	4/2
Mite positive	9	6	8	—
Grass positive	5	3	5	—
Duration of rhinitis (yrs)	11 (4–16)	—	10 (5–15)	—
Duration of asthma (yrs)	8 (4–13)	—	9 (5–14)	—
Duration of OAS	10 (6–19)	13 (9–21)	—	—

Abbreviations: OAS, oral allergy syndrome; AR, allergic rhinitis; A, asthma.

Group A had asthma and rhinitis caused by birch and OAS attributable to golden delicious apple; group B had OAS from golden delicious apple without asthma or rhinitis; group C had asthma and rhinitis because of birch without OAS. Healthy subjects, without a clinical history of allergic conditions and not sensitized (group D) also were studied as controls. Patients had to be nonsmokers and had to not suffer from relevant systemic diseases (eg, hypertension, diabetes, autoimmune diseases). Patients had to be sensitized to birch pollen and to apple as confirmed by skin tests and clinical history. In addition, all patients had to be symptomatic only with apple and had to tolerate other fruits (eg, apricot, cherry, peach, and nuts). Patients with sensitization to mites or animal dander were not admitted. Rhinitis and asthma were diagnosed according to current guidelines,^{10,11} and the symptoms had to be present only during the local birch pollen season. Skin prick tests to inhalant allergens were carried out with a panel of commercial extracts (ALK Abellø, Milan, Italy), including mites, grasses, birch, olive, parietaria, hazelnut, cypress, ragweed, alternaria, and cat and dog dander. They were performed and read according to recommendations.¹²

In most patients, the diagnosis of OAS had been already documented with previous double-blind, placebo-controlled food challenges. In some patients (6/22), a double-blind challenge with grated apple or grated cabbage¹³ was performed to definitely confirm the diagnosis before the study. Sensitization to apple was confirmed by skin prick test with the whole extract and profilin

(ALK Abellø) and by a prick-by-prick with fresh golden apple. The study was performed out of the birch pollen season, and the patients had to be asymptomatic and medication-free at the time of the challenge.

Oral Food Challenge

The oral provocation tests were performed in open fashion, according to Bucher et al.¹⁴ Each apple was washed, and the core and stalks were removed then cut with a maximum share of skin. The patients received increasing amounts of apple, doubling the dose every 5 minutes, starting with 1 g and reaching 128 g (approximately two-thirds of a medium-sized apple). Each test dose had to be chewed before swallowing. The oral cavity was inspected before administering each dose. The oral provocation test was stopped when the patient reported subjective symptoms (itching or burning in the mouth, tongue, or lips) or objective signs (swelling of tongue/lips) appeared, or the maximum test quantity of 128 g was reached.

Measurements

All patients had to rate the severity of their symptoms, either oral (itching or burning in the mouth, tongue, or lips), nasal (itching, sneezing, congestion, rhinorrhea), and conjunctival (itching, lacrimation, burning) on a visual analog scale, from 0 (=absent) to 10 (=very troublesome). A pulmonary function test was carried out before and after challenge with a computerized spirometer (Win-spiro PRO 2.6; Medical International Research Srl, Rome, Italy), and the exhaled nitric oxide (eNO) was measured as well (NIOX MINO, Aerocrine, Sweden) before and 6 hours after the oral specific challenge with apple. Those patients with asthma also completed the Asthma Control Test¹⁵ before the oral challenge. Finally, a nasal eosinophil count was carried out before and 6 hours after the challenge. The samples were collected from the middle third of the inferior turbinate with a Rhino-Probe device (Apotex Scientific, Arlington, Texas), transferred onto a slide glass, air dried, and stained by May Grunwald-Giemsa.¹⁶ A semiquantitative score for eosinophils was assigned according to Meltzer and Jalowayski,¹⁷ from grade 0 (absent) to grade 4+ (covering almost the entire field). The time of 6 hours was chosen to have the reasonable possibility of detecting any change in exhaled nitric oxide and the influx of eosinophils in the nose, if any. Because the normal distribution of the data was not granted, the results were analyzed by the Wil-

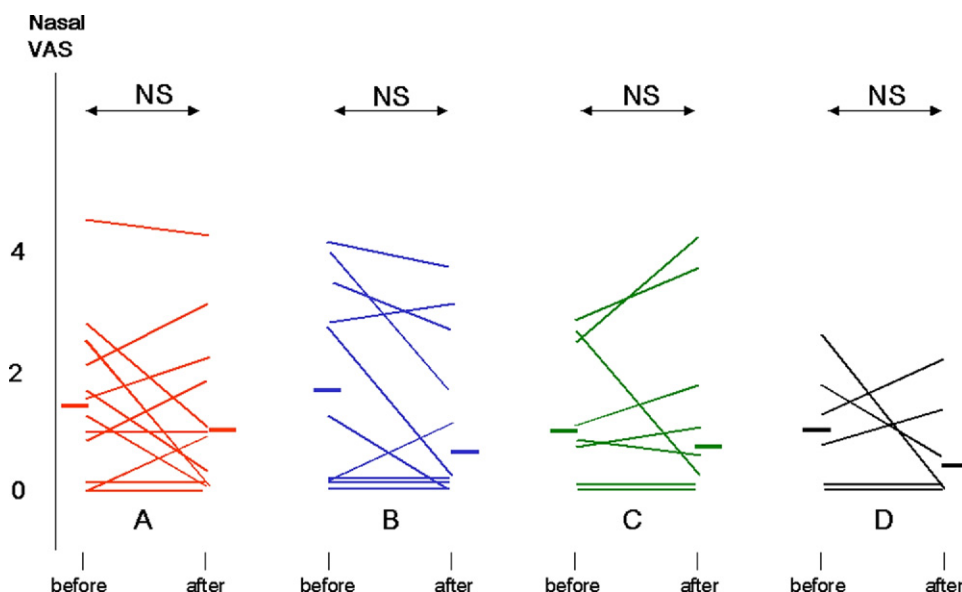


Figure 1. Nasal VAS score before and after challenge in the 4 groups. Medians are indicated as thick horizontal bars.

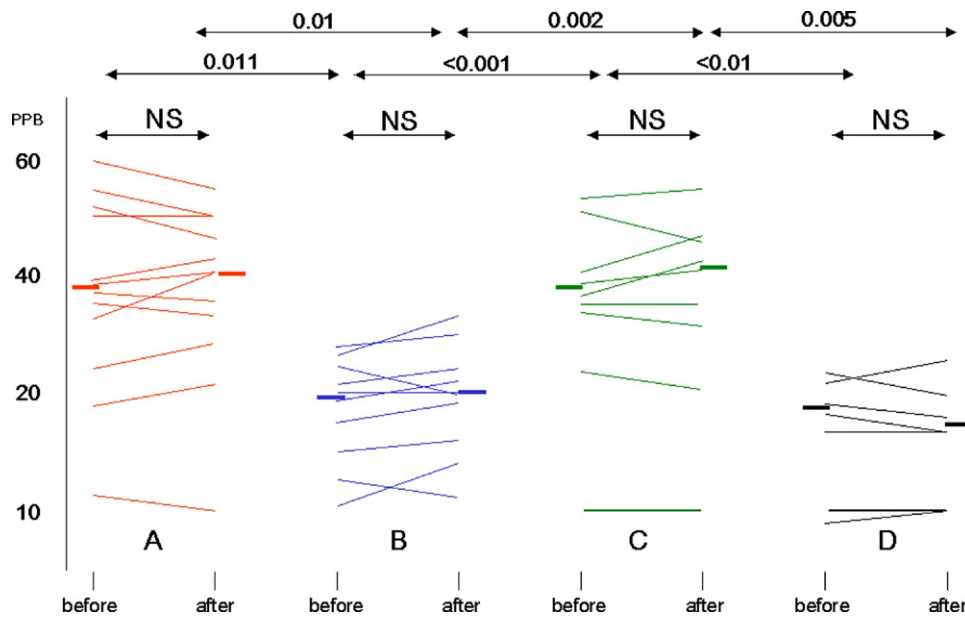


Figure 2. Exhaled nitric oxide (parts per billion) before and after challenge in the 4 groups. Medians are indicated as *thick horizontal bars*. The significant differences are reported above the graphs.

coxon and Mann-Whitney tests (for paired and unpaired samples, respectively) with correction for repeated measures.

Results

Thirty-six subjects who meet the enrollment criteria were studied: 12 had rhinitis plus asthma plus OAS (group A), 10 had OAS alone (group B), 8 had asthma and rhinitis without OAS (group C), and 6 were healthy (group D). Most patients were also sensitized to dust mite and other few allergens, but none had respiratory symptoms out of the birch season. The demographic characteristics are reported in Table 1. All of the patients were symptom-free before the oral challenge, and all of the asthmatic subjects had an asthma control test score greater than 22.

As expected, the VAS scores were low before challenge in all patients. No change occurred in nasal VAS score before versus after challenge in any of the groups (Fig 1), and the same occurred for eye VAS scores (not shown). Also, the intergroup comparisons before and after challenge showed no difference between groups. On the contrary, as expected, in groups A and B, the oral VAS scores significantly increased after challenge. In group A, the median VAS increased from 1 to 8, and in group B from 1.5 to 8.5 ($P < .001$ in both groups). No change was seen in groups C and D. The exhaled nitric oxide showed no change before versus after oral challenge in all groups, as reported in Figure 2, as happened for eosinophils (Table 2). Nonetheless, the values were higher both before and after challenge in groups A and C with respect to groups B and D (Fig 2). As far as forced expiratory volume in 1 second, in this case no significant difference was seen before versus after challenge, nor when comparing the groups (Fig 3). The forced vital capacity before and after challenge, was 4.13 ± 0.81 L ($95\% \pm 8\%$ predicted) and 4.32 ± 0.85 L ($98\% \pm 10\%$ predicted) in group A, 3.87 ± 0.81 L ($98\% \pm 9\%$) and 3.86 ± 0.83 L ($97\% \pm 7\%$) in group B, 3.16 ± 0.54 L ($94\% \pm 10\%$) and 3.18 ± 0.54 L ($95\% \pm 11\%$) in group C, 3.73 ± 1.21 L ($101\% \pm 11\%$) and 3.59 ± 1.61 L ($102\% \pm 9\%$) in group D, with no significant intra- or inter-group difference.

Discussion

Mucosal lining of respiratory and upper gastrointestinal tracts have a common embryonic origin,^{6,18} and the distribution of mast cells, which initiate the allergic reaction, is quite similar in the 2

compartments. This is testified by the well-known phenomenon of OAS, which represents an allergen-driven mast cell activation in the mouth after the contact of food-derived allergens. In this case, the birch-apple syndrome is a paradigm of the similar reactivity of respiratory and oral mucosae.^{19,20} Despite our knowledge of the mechanisms of asthma, rhinitis, OAS, and united airways disease, no data are available on the possible functional interactions among the different diseases and anatomical compartments.

Therefore, we attempted to assess whether a functional relationship exists between the digestive and the respiratory tract, by studying patients with OAS and respiratory allergy after an oral challenge with apple. To ensure an adequate provocation, a very high amount of apple was administered (128 g). Despite this, and despite the appearance of OAS symptoms in all patients, no appreciable change was found in respiratory functional parameters, namely nasal eosinophils, exhaled nitric oxide, respiratory symptoms, and respiratory function. Because the study was performed out of the birch pollen season, the confounding factor of the environmental allergen load could be avoided, this making the model as “clean” as possible. Under the current experimental conditions, and with the inherent limitation of the open challenge model, the respiratory and upper digestive tract seem to be functionally independent, as far as the allergic reaction is concerned. A possible

Table 2
Nasal Eosinophils before and after Challenge

	Group A		Group B		Group C		Group D	
	Before	After	Before	After	Before	After	Before	After
1	2+	2+	1+	0	2+	2+	1+	1+
2	2+	3+	0	2+	1+	1+	0	0
3	2+	1+	0	0	0	1+	0	0
4	0	1+	1+	1+	3+	2+	2+	1+
5	2+	1+	1+	0	2+	0	1+	1+
6	1+	0	2+	1+	1+	2+	1+	2+
7	1+	0	0	1+	2+	1+		
8	1+	2+	2+	2+	1+	1+		
9	1+	1+	0	0				
10	0	0	1+	2+				
11	2+	2+						
12	1+	1+						

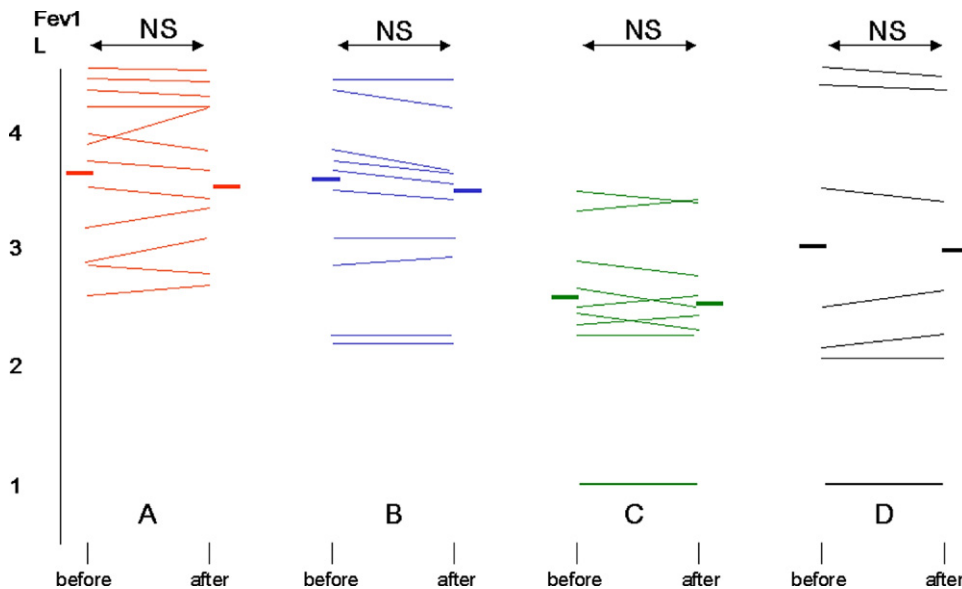


Figure 3. Forced expiratory volume in 1 second in liters before and after challenge in the 4 groups. Medians are indicated as thick horizontal bars.

explanation of this fact may be the nature of the allergen involved (Mal d 1, Bet v 1 homolog), which has been demonstrated to not be able to elicit symptoms when directly applied in the respiratory tract.²¹ Conversely, the clinical model of eosinophilic esophagitis would support a functional link between respiratory allergy and immunological responses in the digestive tract,²² although the observations in this regard are not always consistent. In summary, in the case of birch-apple syndrome, the simple ingestion of the culprit food does not imply a risk for respiratory reactions.

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