

DR. MARIE LAGREULA (Orcid ID : 0000-0003-3736-7116)

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Risk factors for developing food-induced bronchospasm during oral food challenge

Authors: Marie LAGREULA^a, Anca-Mirela CHIRIAC^{a,c}, Maria Chiara LEONI^{a,b}, Pascal DEMOLY^{a,c}, Davide CAIMMI^{a,c}

Affiliations:

^a Department of Pulmonology, Division of Allergy, Hôpital Arnaud de Villeneuve, University Hospital of Montpellier, Montpellier, France;

^b Pediatric Unit, Centre Hospitalier Intercommunal de Créteil; Créteil, France.

^c UPMC Univ Paris 06, UMRS 1136, Equipe - EPAR - IPLESP, Sorbonne Universités, Paris, France.

Running title: Bronchospasm as a food allergy symptom

Corresponding Author: Marie LAGREULA, MD

Unité d'allergologie – CHU de Montpellier (France)

371, Avenue du Doyen Gaston Giraud – 34090 Montpellier (France)

Phone number: 0033467336112

E-mail: marie.lagreula@gmail.com

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To the Editor:

Prevalence of both asthma and food allergy is increasing in Western Europe (1,2). In France, according to recent surveys, the prevalence of asthma is 9.4% in children and 7% in adults (3). Food allergy proven by oral food challenges (OFC) affects between 1 to 10% of the population (4). Studies have been considering both disorders as comorbidities under the atopic disease concept. Asthmatic children with food allergy have an increased risk for asthma exacerbation and severe asthma, especially when developing anaphylactic reactions (1,5). Each part of the respiratory system (the nose, the larynx, and the lungs) may be involved in food-induced allergic reactions, especially in IgE-mediated allergic reactions, and food allergies play a role in the pathogenesis of respiratory tract symptoms (6).

Bronchospasm caused by food allergy is a condition that may be elicited by either ingestion or inhalation of food allergens. Little is known about the frequency or the risk factors of food-induced bronchospasm.

The aim of the present study was to establish the frequency of bronchospasm during positive OFC and to identify possible risks factors.

We conducted a retrospective study including all consecutive patients aged 5 years and older, with a positive OFC to any food, investigated at the Allergy Unit of the University Hospital of Montpellier, France, from January 2001 to January 2016, without discriminating if they suffered or not from asthma.

Prior to OFC, in order to conduct a complete allergy work-up and to reach a proper diagnosis, we collected for each patient the clinical history and looked for positive skin prick tests (SPT) and/or serum specific IgE (ImmunoCAP Phadia, Thermo Fisher Scientific®). To increase the sensitivity of SPT, skin tests were performed with the standardized extract (if available), as well as with the native food. All *in vivo* methods followed the EAACI recommendations for OFC (7). The cut-off used for positive serum specific IgE was 0.10 kU/L. To standardize the classification of allergic reactions reported by patients and during OFC we used Sampson's classification for anaphylaxis (8). Adequately trained personnel performed pulmonary function testing (PFT) in each patient, before and after OFC (and if needed and possible, during OFC), through spirometry. Diagnosis of bronchospasm was based on both clinical criteria and PFT results, obtained at the time the reaction unless the clinical emergency did not allow performing a spirometry at that time. Clinical criteria and spirometric parameters were recorded following current guidelines (9). Several possible risk factors of bronchospasm during OFC were evaluated: age at OFC, gender, presence of pre-existent asthma, tested food, severity of the index allergic reaction, presence of bronchospasm at index reaction, allergen specific IgE levels (source and proteins when available), delay between the time of the last ingested dose during OFC and the onset of the reaction, family history of atopy, symptomatic sensitizations, association with allergic rhinitis (AR), with atopic dermatitis (AD), and diagnosis of multiple food allergy. All patients or their legal representatives were informed about the benefits and risks of OFC and signed an informed consent form. The study was approved by the local and national regulatory agencies (Comité de Protection des Personnes Sud Méditerranée V and Agence Nationale de Sécurité du Médicament).

The frequency of bronchospasm during OFC was expressed in percentage with a 95% confidence interval (CI). The quantitative variables distribution was assessed by the Shapiro-Wilk test (non-normal distribution) and presented as medians and interquartile intervals. As for qualitative variables, data were expressed in percentages and the independent chi2 test or Fisher's exact test were used for comparisons between the two groups (patients with bronchospasm versus without bronchospasm). To

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assess risk factors of food-induced bronchospasm, we carried out logistic regression modelling (univariate then multivariate analysis; independent variables with $p \leq 0.25$ were kept for multivariate modelling). A p -value < 0.05 was considered as significant. Statistical analysis was conducted with SAS (SAS University Edition). We performed a regression tree model to predict the risk of bronchospasm during OFC (Classification and Regression Tree method, rpart in R, version R 3.2.2). Decision trees are represented by a set of questions which split the learning sample into smaller and smaller parts, called nodes. CART asks only yes/no questions. CART algorithm searches for all possible variables and all possible values in order to find the best split (i.e., to ideally have « pure » terminal nodes, where one class dominates, e.g., bronchospasm/not bronchospasm). All independent variables mentioned above were used in this model. A cross-validation (with repeated random sub-sampling) was performed, to assess the robustness of the results.

A total of 126 patients, accounting for 147 positive OFC were included. Among them, 82 (66.7%) patients had a previous diagnosis of asthma (Figure 1). Median age was 10 years [7-14]; 73 (58%) were males, 108 (86%) were children, and 18 (14%) adults; 94 (75%) suffered from AR, 61 (50%) from AD and 66 (53%) presented multiple food allergies. Thirty-one different foods were tested, the three most frequent being peanut (22%), egg (14%) and cow's milk(5%) (the others were: tree nut, fruits, fish, vegetables, shellfish, legumes). Characteristics of the allergic reactions are shown in Table 1. As shown in Figure 1, in 44 (29.9%) out of all 147 positive OFC we recorded a bronchospasm. Considering the whole cohort of 126 included patients, forty-two (33.3%) developed a bronchospasm during the OFC, and, in this last group, most patients (36.4%) were tested for peanuts. Among the 44 OFC with bronchospasm, 9 had an isolated bronchospasm and the others experienced an anaphylactic reaction including bronchospasm. There was no significant difference regarding demographic data, comorbidities between the two groups with or without bronchospasm (Table 1). The median value of specific IgE levels was 2, and no significant difference between the two groups was found ($p=0.1$). The multivariate logistic regression found peanut allergic reaction as the only risk factor for food-induced bronchospasm (OR= 2.92 [1.28-6.02], $p=0.01$). Regarding the algorithm established by the regression tree (Figure 2), the most relevant predictive combination of food-induced bronchospasm

was a clinical history of grade 2 to 4, anaphylaxis to milk or peanut confirmed by OFC, and children younger than 9.5 years (sensitivity 87%, specificity 79%).

We found that almost one third of the evaluated allergic patients (and up to 35% of children) developed a bronchospasm during OFC. These results are much higher if compared with a cohort of only asthmatic children suffering from food allergy as well, highlighted by a recent review, that recorded 2-9% of asthma exacerbation elicited by OFC (1). In a paper by Yazicioglu et al., only 2 patients reported bronchospasm during OFC, but the Authors evaluated only egg and milk allergy in children aged between 1 and 6 years old, and diagnosis was reached without performing PFTs, because of the age of the patients (10). The different criteria for asthma diagnosis and the different characteristics of the included cohorts, as well as the small number of investigated subjects per study, may account for the discrepancy in the results. Moreover, these two studies did not include patients undergoing OFC to peanut, that was actually the only risk factor for bronchospasm during OFC. Our results were similar to those highlighted/found by Bock et al. (11).

The pathophysiology of food-induced bronchospasm is still unknown. Krogulska et al. showed that non-asthmatic children suffering from food allergy had increased bronchial hyperreactivity, proved by methacholine inhalation challenge, despite a lack of evident clinical and spirometric signs of bronchospasm after OFC (12,13). These children would therefore be more prone to develop a bronchospasm during an allergic reaction in real-life. This bronchospasm would manifest only in relation to exposure to the food, in a similar way of allergic asthma to pollens. It remains unclear if such clinical entity might be considered as a distinct asthma phenotype.

In our study, the multi-variate logistic regression showed that pre-existent asthma was not a risk factor of food-induced bronchospasm during OFC. Moreover, some food allergic children developed bronchospasm although they did not have previous diagnosis (nor signs or symptoms) of asthma. Although we did not consider a respiratory follow-up of these patients, these food allergic children could be considered as belonging to a new specific asthma phenotype, that could be “allergic patients with food-induced asthma”. Respiratory signs during the index food reaction was not found as risk

factor in the multivariate model, may be because initial diagnosis of bronchospasm on the index reaction was based only on reported symptom, but we can't excluded a lack of power of our study.

Reactions to peanuts were found to be the only independent risk factor to develop a bronchospasm during OFC on a multivariate analysis. Being allergic to peanut increased 3-folds the risk of peanut-induced bronchospasm. However, peanut poly-allergic patients did not have an increased risk of food-induced bronchospasm when reacting to other food allergens. Thirteen peanut allergic patients underwent a positive OFC with another food, and among them, 7 developed a bronchospasm with the other allergen, while 6 did not. Peanut allergy was already found as risk factor of asthma exacerbation in asthmatic children (1). Children allergic to peanuts should be considered not only at risk of severe anaphylaxis, as it is well known, but also at high risk of food-induced bronchospasm. Therefore, physicians should take this risk into account when prescribing emergency kits. Other studies that included asthmatic children, found other foods as relevant risk factors of food-induced bronchospasm (1): egg, cow's milk, wheat, soy, fish, shrimp, celery. In our study, we only tested 8 and 22 patients for cow's milk and egg, respectively. The association between asthma and multiple food allergies was found in certain studies (1) but not ours, as a risk factor of severe asthma, especially in patients with partially controlled asthma. In our study, all included asthmatic patients presented with a controlled asthma before the OFC and one third of our patients didn't suffer from pre-existent asthma.

Our regression tree found a combination of three clinical characteristics to approach patients at risk of food-induced bronchospasm: age below 9.5 years, allergic reaction to peanut or cow's milk, and grade 2 to 4 as for the severity of the index reaction. Nevertheless, cross-validation found that 40% of patients were misclassified, making it difficult to routinely use this decision tree in clinical practice. However, the regression tree showed a sensitivity of 87%, and we decided to perform a prospective study (NCT02884583) on a new cohort of patients to investigate the pathophysiology of food-induced bronchospasm. In the first four patients with a positive OFC included in the prospective phase, none developed bronchospasm, but they could all be correctly classified in the predictive tree (unpublished data).

Our study was conducted in a single centre, which could be considered as a selection bias. However, the repartition of proven food allergy in our patients was close to other French data (14). Because our sample was rather small (126 patients), the risk factor assessment was limited and some risk factors found in other studies were not confirmed in our cohort. Another limitation of our study concerns the diagnosis of bronchospasm during OFC. In 10 cases (6.8%), spirometry was not performed during the OFC, the reaction needing to be treated in emergency. The diagnosis of bronchospasm was then made based on the symptoms presented by the patients. Finally, it should be underlined that we evaluated the appearance of bronchospasm during OFC, which is different from what people experience in “real life”, when consumed doses and cofactors could change the thresholds, symptoms and the conditions of reactivity.

In conclusion, we found that almost one third of our food allergic patients develops food-induced bronchospasm, with a high risk for peanut allergy. These results should be confirmed by other studies, but suggest that the management of food allergic patients must take into account the risk of bronchospasm, even in non-asthmatic patients, especially if suffering from peanut allergy.

Marie LAGREULA, MD, Montpellier (France)
Anca-Mirela CHIRIAC, MD, Montpellier (France)
Maria Chiara LEONI, MD, Creteil (France)
Pascal DEMOLY, PhD, Montpellier (France)
Davide CAIMMI, MD, Montpellier (France)

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Table 1 – Allergic profile of the included population.

	Positive OFC	Appearance of bronchospasm during OFC	Without bronchospasm during OFC	<i>p-value</i>
	Total N = 147 N (%)	N = 44 (29.9%) N (%)	N = 103 (30.1%) N (%)	
Allergen				0.04 [#]
Peanut	33 (22.4%)	16 (48.5%)	17 (51.5%)	
Egg	22 (15.0%)	4 (18.2%)	18 (81.8%)	
Cow's milk	8 (5.4%)	3 (37.5%)	5 (62.5%)	
Other	84 (57.1%)	21 (25.0%)	63 (75.0%)	
Severity of the reported reaction*				0.12 [#]
A	50 (34.0%)	12 (24.0%)	38 (76.0%)	
B	51 (34.7%)	13 (25.5%)	38 (74.5%)	
C	46 (31.3%)	19 (41.3%)	27 (58.7%)	
Bronchospasm during Index reaction**				0.13 [#]
No	103 (70.1%)	17 (16.5%)	86 (83.5%)	
Yes	44 (29.9%)	12 (27.3%)	32 (72.7%)	
Other atopic Disease⁽ⁱ⁾				0.60 [#]
No	5 (3.4%)	1 (20.0%)	4 (80.0%)	
Yes	141 (95.9%)	43 (30.5%)	98 (69.5%)	
No data	1 (0.7%)			
Delay of the reaction⁽ⁱⁱ⁾				0.27 [#]
< 60 minutes	8 (5.4%)	43 (30.9%)	96 (69.1%)	
> 60 minutes	139 (94.6%)	1 (12.5%)	7 (87.5%)	

Chi2 test

* Grade of reaction during the index reaction with the tested food:

A= Skin reaction or isolated vomiting;

B= anaphylactic reaction: 33 (22.7%) anaphylactic reaction grade 2, 11 (7.5%) anaphylactic reaction grade 3, 0 anaphylactic reaction grade 4;

C= avoidance based on positive skin prick test

** Bronchospasm during index reported allergic reaction with the food tested during the OFC.

⁽ⁱ⁾ Allergic rhinitis or atopic dermatitis, or other food allergy

⁽ⁱⁱ⁾ Delay between the last dose of food during the OFC and the beginning of the reaction

Figure 1 – Flow-chart of food allergic patients and OFC with and without bronchospasm

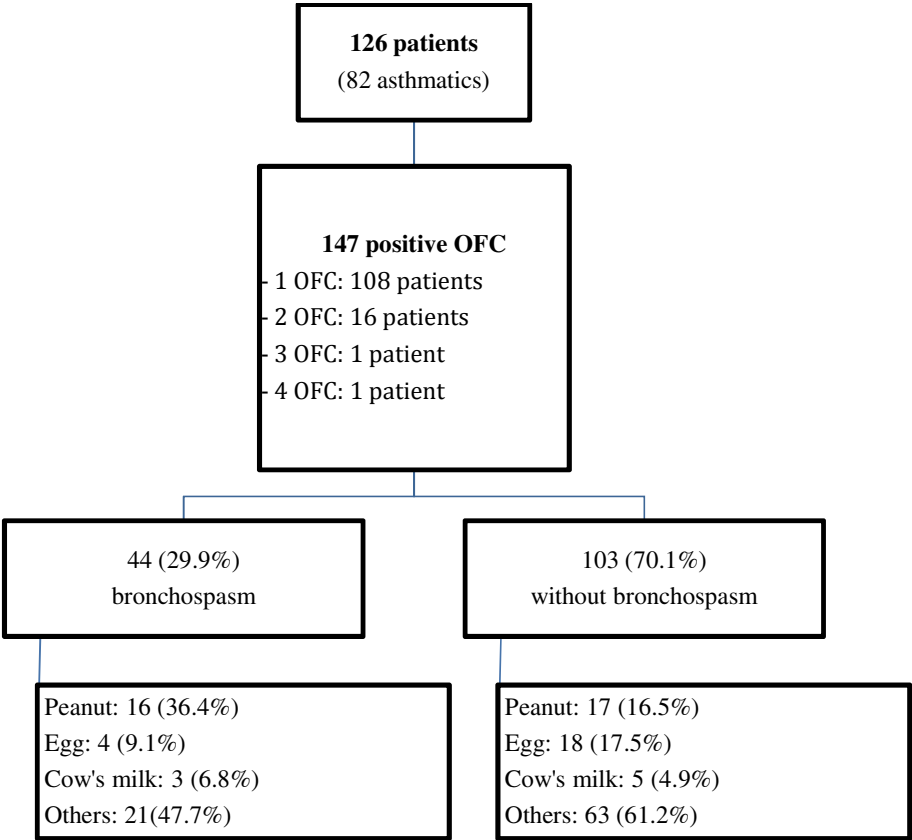


Figure 2 – Predictive algorithm for bronchospasm induced during positive food challenge.

The number of well classified and misclassified is presented in each terminal node: Number of patient with no bronchospasm/number of patient with bronchospasm)

