

Food Allergy in Children with Asthma: Prevalence and Correlation with Clinical Severity of Respiratory Disease

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Abstract: Epidemiological evidence suggests that there is a link between asthma and food allergy. The aim of this study was to estimate the prevalence of food allergy in asthmatic children and to evaluate a possible impact of food allergy on asthma severity. The study enrolled 103 asthmatic children (mean age: 11 years). Skin prick-test, dosage of specific IgE to a standardized panel of inhalant and food allergens and spirometric evaluation was made for each patient. Twenty-four (23%) patients presented food allergy, 75 (77%) were sensitized to at least one food. A lower rate of children with controlled symptoms was found in children with food allergy and a higher rate of persistent asthma was found in children sensitized to at least 4 foods. In conclusion, food allergy/sensitization should always be investigated in asthmatic children for its association with increasing severity (only in food sensitized patients) and reduced control of asthmatic symptoms.

Keywords: Asthma, food allergy, oral allergy syndrome.

INTRODUCTION

Allergic diseases have increased over the last years, as many epidemiological studies confirm. Food allergy is often the first manifestation of allergy in childhood: it occurs in 6% to 8% of the paediatric population younger than 3 years and 2% to 3% of the general paediatric population [1]. In young children, foods responsible for the vast majority of reactions are milk, egg, peanut, tree nuts, fish and shellfish.

Allergic reactions after ingestion of raw vegetables and fruits are also common, and may provoke both mild (such as 'oral allergy syndrome') than more severe reactions.

Early childhood allergies to milk, egg, soy and wheat usually resolve by school age (80% of cases); peanut, tree nut and seafood allergy are usually considered permanent [2]. Epidemiological evidence suggests that there is a link between asthma and food allergy. The statistical association between these two allergic diseases may be due to their common atopic basis or may reflect a close inter-relationship in their pathogenesis [3].

Asthma is considered the most frequent pulmonary disease in infancy [4] and is a significant cause of morbidity and mortality in the paediatric population, especially in the inner-city [5].

Although many studies have shown an association between food allergy and respiratory allergy (e.g. oral allergy syndrome in pollinosis), the true prevalence of food allergy in the population with asthma is unknown. In 1988, Novembre *et al.* [6], found that out of 140 asthmatic children (range: 2-9 years), 48 (34%) presented a referred history of food allergy, but this was confirmed by food challenges in only 16 cases (11.4%). Another paper [7] investigated the prevalence of food allergy in 6672 schoolchildren aged 9-11

years recruited from 108 schools randomly selected in six French cities: of the children with asthma and concomitant allergic rhinitis, 6.4% reported symptoms of food allergy and 4.5% were sensitized to food allergens; of the children with only asthma, 2.9% reported symptoms of food allergy and 3.2% were sensitized to food allergens. However, more recent studies estimated that 4% to 8% of children with asthma have coexistent food allergy [8,9].

In recent years, some authors have focused on the possible link between food allergy and asthma severity [10,11].

Wang *et al.* [11] investigated the degree of food allergen sensitization in 504 sera from inner-city children with asthma (mean age: 6 years; range: 4-9) enrolled from emergency departments and clinics in inner-city areas in United States and evaluated the impact of food sensitization on asthma morbidity. In the group (45% children) sensitized against at least one food allergen, the authors found a higher rate of hospitalisation ($p < 0.01$) and required more steroid medications ($p = 0.025$) than non-sensitized individuals.

In a case-controlled study [10], food allergy was found to be a significant risk factor ($p = 0.006$) for life-threatening asthma: out of 54 asthmatic children (range: 1-16 years), the prevalence of food allergy was higher (10 cases; 52.6%) in 19 children ventilated for a life threatening asthma, than in controls with mild asthma (4 cases; 10.5%).

This study was performed with the aim to estimate the real prevalence of food allergy and food allergen sensitization in asthmatic children and to evaluate a possible impact of food allergy on the severity and control of respiratory disease.

MATERIALS AND METHODOLOGY

Subjects

The study involved 103 children (69 males and 34 females) with a mean age of 11 years, (range 7-19 years) referred to the Allergologic Center of the Pediatric Department

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of Bologna University. For inclusion all patients had to have a clinical history of inhalant allergen-induced asthma (with or without associated allergic rhinitis). Inhalant allergen sensitization was defined by skin prick test (Lofarma, Milan; Italy). Classification of severity of asthma (intermittent, mild persistent, moderate persistent, severe persistent) was evaluated according to criteria provided by GINA guidelines [12]. All patients were allowed to take medications (oral/topic antihistamines, nasal corticosteroids, inhaled corticosteroids in association or not with long-acting or short-acting β_2 -agonists) according to grade of severity of asthma and rhinoconjunctivitis when associated (GINA and ARIA guidelines [12,13]).

This research was conducted in accordance with the principles of the Declaration of Helsinki; informed consent was obtained by children and their parents.

Skin Prick-Test

At enrolment all patients were given the skin-prick test (SPT) with a panel of allergenic extracts (Lofarma, Milan; Italy): timothy grass pollen, birch tree pollen (*Betula verucosa*), hazel tree pollen (*Corylus avellana*), olive-tree (*Olea*), wall pellitory (*Parietaria*), Alternaria, cat, dog, dust mite (*D. pteronyssinus*, *D. farinae*), egg, milk, soy, wheat, fish, peanut, hazelnut, apple and kiwi.

A SPT result was considered positive when a wheal of at least 3 mm greater than the negative control was recorded 15 min after the application of the test.

In Vitro Test

Specific IgE (sIgE) were detected by the means of the CAP system (UniCAP 1000, Phadia, Sweden).

The sera of six patients were not available at enrolment: only 97/103 sera were analyzed.

All sera were performed with a panel of allergenic extracts: timothy grass pollen (*Phleum pratense* and *Cynodon dactylon*), birch tree pollen (*Betula verucosa*), hazel tree pollen (*Corylus avellana*), olive-tree (*Olea*), wall pellitory (*Parietaria*), Alternaria, cat, dog, dust mite (*D. pteronyssinus*, *D. farinae*), egg, milk, soy, wheat, fish, peanut, hazelnut, apple and kiwi.

Values of specific IgE greater than 0.35 kU/L were considered positive.

Follow-Up of Respiratory Disease

All patients underwent at least three spirometric tests (ZAN100 Rhino FLOWHANDY II; Zan Ferraris; Germany): at enrolment (t_0) and at six (t_1) and 12 months (t_2) after enrolment. Lung volumes (FVC, FEV₁, FEV₁/FVC, PEF 25-75) were recorded before and 15 minutes after the inhalation of a dose of short-acting β_2 -agonist (salbutamol: 200 μ g).

Evaluation of asthma control was performed at t_0 , t_1 and t_2 : asthma was defined as controlled, partially controlled and uncontrolled [12,14].

Food Allergy Diagnosis

All patients were evaluated for the presence of food allergy.

All subjects were questioned about symptoms of food allergy and age of onset of symptoms.

Food allergy was defined as certain in patients with positive open food challenge and a convincing clinical history of acute reactions with a documented level of specific IgE against the food considered [15, 16].

Food allergy was defined as probable in patients who had not performed oral challenge, but reported a clinical history suggestive for food allergy and a level of specific IgE with positive predictive value (PPV) > 95% for the food considered, according to PPV values indicated by Sampson [17].

Statistical Methods

Data were stored by means of customized databases. Statistical analyses were carried out by means of the Statistical Package for Social Science (SPSS/PC; SPSS Inc., Chicago, IL, USA). The Chi-square test and the Student *t*-test were applied where appropriate. In particular, proportions were compared by Chi-square test; geometric mean levels of specific and total IgE were compared by Student *t*-test.

Probability (*p*) values of less than 0.05 were considered significant.

RESULTS

At enrolment 59 patients (58%) had intermittent asthma, 33 (32%) mild persistent asthma, 10 (10%) moderate asthma and only one patient severe asthma.

During the 1-year follow-up, 23 patients (22%) presented a total control of asthma symptoms, 71 (69%) partly control and 9 (9%) no control. Mean age of onset of asthmatic symptoms was 7 years.

The prevalence of food allergy, allergic rhinitis, atopic eczema and age of onset of clinical manifestations are shown in Table 1. Eighty-seven (84%) patients had grass pollen allergy, 36 (35%) house dust mite allergy, 11 (11%) cat dander allergy, 3 (3%) birch pollen allergy, 2 (2%) dog dander allergy, 2 (2%) hazel pollen allergy. Twenty-three (22%) patients were allergic to both grass pollen and house dust mite.

Of the 97 sera available, 89 (92%) were positive to grass pollen and 61 (63%) to both birch and grass pollen. All patients sensitized to birch pollen were also sensitized to grass pollen.

Table 1. Prevalence of Asthma, Allergic Rhinitis, Food Allergy, Atopic Eczema and Respective Diseases and Age of Onset of Clinical Manifestations in 103 Children with Allergic Asthma

| Disease | Mean Age of Onset | Lifetime N (%) | Past N (%) |
|-------------------|-------------------|----------------|------------|
| Asthma | 7 years | 103 (100) | - |
| Allergic Rhinitis | 6 years | 70 (68) | - |
| Food Allergy | 2 years | 24 (23) | 9 (9) |
| Atopic Eczema | 8 months | 16 (15) | 29 (28) |

Food Allergen Sensitization

Seventy-five (77%) subjects were sensitized against at least one food allergen.

The prevalence and level of sensitization against each food allergen tested is shown in Table 2.

Table 2. Prevalence and Level of Sensitization Against Food Allergen Tested in Sera of 97 Asthmatic Children

| Food | Presence of Sensitization n (%) | Presence of Patients with >95% Positive Predictive Level* | Geometric Mean sIgE (kU/L) | Range of sIgE (kU/L) | Presence of Patients with Food Allergy n |
|--------|---------------------------------|---|----------------------------|----------------------|--|
| Egg | 29 (30) | 5 | 1.4 | 0.39-36.3 | 9 |
| Milk | 27 (28) | 1 | 1.7 | 0.38->100 | 4 |
| Fish | 11 (11) | 1 | 1.4 | 0.36->100 | 4 |
| Peanut | 64 (66) | 14 | 1.9 | 0.35-42.1 | 14 |
| Soy | 49 (50) | 0 | 2.15 | 0.36-17.5 | 0 |
| Wheat | 65 (67) | 0 | 2.4 | 0.3-31 | 0 |

*According to Sampson [17].

Most of the children were sensitized against plant foods, such as wheat (65 cases; 67%), peanut (64 cases; 66%) and soy (49 cases; 50%). Less than half of the sera were positive to animal derived foods, such as egg (29 cases; 30%), milk (27 cases; 28%) and fish (11 cases; 11%). Fourteen patients presented a >95% positive predictive level of specific IgE according to values determined by Sampson [17] against peanut. Of these subjects one had the food allergy confirmed in food challenge, one had never eaten peanuts due to the persistence of high values of specific IgE, and one had outgrown peanut allergy. Eleven children out of 14 with >95% positive predictive level of specific IgE against peanuts were able to eat peanuts without any adverse reaction.

Specific IgE against milk and fish presented a wide range (even values > 100 kU/L).

Food Allergy and Correlated Symptoms

Twenty-four children (23%) had food allergy; in 21 cases diagnosis was confirmed in oral challenge. Mean age of onset of food allergy (for the first food) was about 2 years (mean value). Of the 24 children with food allergy, the most frequent foods responsible for clinical manifestations (also in association) are: egg (9 cases; 12%), hazelnut (7 cases; 9%), peanut and kiwi (6 cases; 8%), milk, fish, tomato and apple (4 cases; 5%), banana, water-melon, peach (3 cases; 4%), walnuts, pepper, carrot, peas, beans, cherry and apricot in 2 cases (3%), almonds, egg-plant, fennel, strawberry, melon, pineapple and orange one case (1%). Two cases of reported anaphylactic shock had been induced by tree nut in one case and egg in the other. Clinical manifestations of food allergy were reported only by 21 subjects with food allergy confirmed by food challenge (Table 3). Thirteen subjects (62%) presented oral allergy syndrome, 7 (33%) respiratory symptoms (asthma or rhinitis), 7 (33%) gastrointestinal symptoms (nausea, vomiting, diarrhoea) and 7 (33%) symptoms limited to skin (eczema, urticaria). Only two children (10%) reported anaphylactic shock. Food allergy induced asthma was seen only in 6 cases (29%). Symptoms and respective eliciting food are summarized in Table 4. Oral allergy syndrome, rhinitis and urticaria were provoked by ingestion of vegetables or fruits. Seven children (33%) out of 21 with food allergy confirmed by oral challenge presented oral allergy syndrome after ingestion of fruit or other raw vegetables. Four children (19%) had oral allergy syndrome after ingestion of hazelnut. Gastrointestinal symptoms were associated with egg and fish.

Table 3. Clinical Manifestations of Food Allergy in 21 Asthmatic Children with Food Allergy Confirmed by Food Challenge

| Symptom | Number of Subjects (%) |
|---|------------------------|
| Oral Allergy Syndrome | 13 (62) |
| Gastrointestinal Symptoms (nausea, vomiting, diarrhoea) | 7 (33) |
| Asthma (cough, wheeze) | 6 (29) |
| Urticaria | 4 (19) |
| Atopic Eczema | 3 (14) |
| Anaphylaxis | 2 (5) |
| Rhinitis | 1 (10) |

Table 4. Clinical Symptoms, According to Food Allergens, in 21 Asthmatic Children with Food Allergy Confirmed by Food Challenge

| Symptom | M | E | F | P | L | H | N | V/F |
|---|---|---|---|---|---|---|---|-----|
| Oral Allergy Syndrome | 1 | 1 | 1 | 1 | 1 | 4 | 1 | 7 |
| Gastrointestinal Symptoms (nausea, vomiting, diarrhoea) | 0 | 4 | 2 | 0 | 0 | 1 | 0 | 0 |
| Asthma (cough, wheeze) | 2 | 1 | 0 | 2 | 0 | 2 | 0 | 0 |
| Urticaria | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 2 |
| Atopic Eczema | 2 | 2 | 0 | 1 | 0 | 1 | 0 | 0 |
| Anaphylaxis | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 0 |
| Rhinitis | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 |

M= Milk; E= Egg; F= Fish; P= Peanut; L= Legumes; H= Hazelnut; W= Walnut; V/F= Vegetables/Fruits.

Food Allergy and Severity and Control of Respiratory Disease

In Table 5 (Fig. 1) the relationship between food allergy and severity and control of respiratory disease is shown. There was no significant difference in the degree of severity of asthma among subjects affected or not by food allergy. In contrast, children without food allergy presented a higher rate of controlled asthma (25%) than children with food allergy (only 12%).

Finally, a possible association between severity and/or control of asthmatic symptoms and presence of sensitization against food allergens (with or without symptoms of food allergy) was analysed. As shown in Table 6 (Fig. 2), subjects sensitized to at least four food allergens had a higher rate, though not significant (24 cases; 48%), of persistent asthma (mild, moderate or severe) than children sensitized to no more than 3 food allergens (9 cases; 36%), and than the children without any sensitization to food allergens (7 cases; 31%). Moreover the children without food allergen sensitization or sensitized to up to 3 food allergens, presented a higher rate of controlled asthma (23% in children without food allergen sensitisation and 36% in children sensitized to up to 3 food allergens) than children sensitized to at least 4 foods (only 16%).

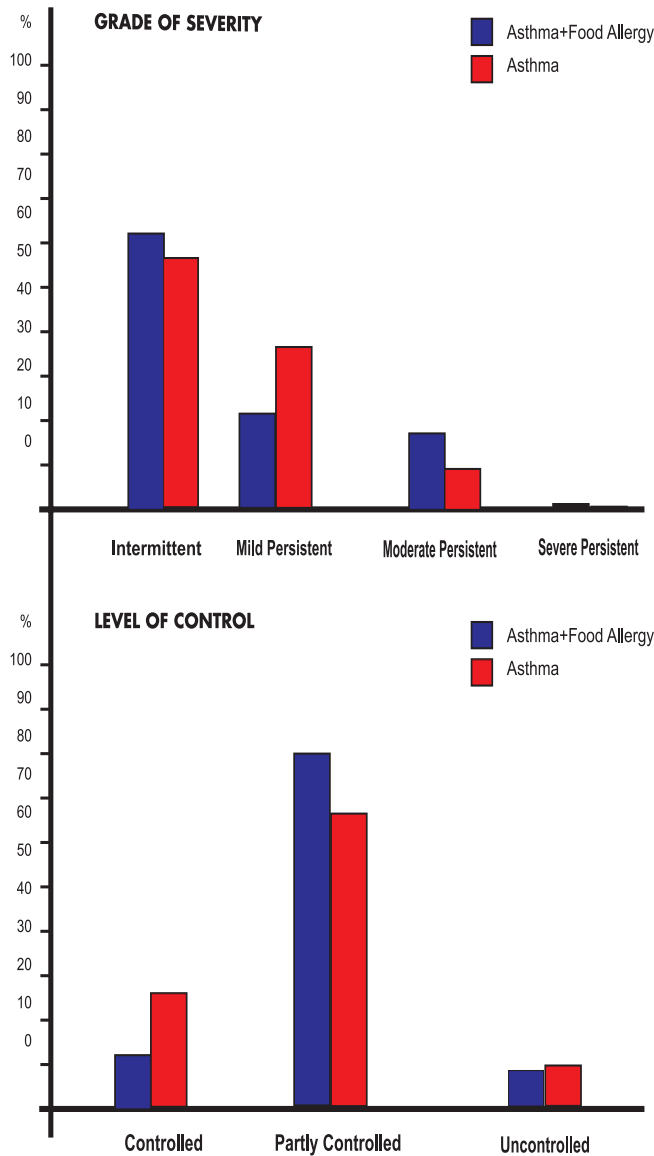


Fig. (1). Correlation between food allergy and severity and control of asthma in 103 asthmatic children.

DISCUSSION

The aim of this study was to determine the prevalence of food allergy in a population of asthmatic children and a pos-

sible influence of food allergy on asthma severity and/or control.

Table 5. Correlation Between Food Allergy and Severity and Control of Asthma in 103 Asthmatic Children

| | > 3 Food Allergens N=50 (%) | ≤ 3 Food Allergens N=25 (%) | No Food Allergen Sensitization N=22 (%) |
|--------------------------|-----------------------------|-----------------------------|---|
| GRADE OF SEVERITY | | | |
| Intermittent | 26 (52) | 16 (64) | 15 (68) |
| Persistent mild | 17 (34) | 7 (28) | 5 (23) |
| Persistent moderate | 6 (12) | 2 (8) | 2 (9) |
| Persistent severe | 1 (2) | 0 | 0 |
| LEVEL OF CONTROL | | | |
| Controlled | 8 (16) | 9 (36) | 5 (23) |
| Partially controlled | 35 (70) | 15 (60) | 16 (73) |
| Uncontrolled | 7 (14) | 1 (4) | 1 (4) |

Table 6. Correlation Between Sensitization to Food Allergens and Severity and Control of Asthma in 97 Asthmatic Children

| | Asthma+Food Allergy N=24 (%) | Asthma N=79 (%) |
|--------------------------|------------------------------|-----------------|
| GRADE OF SEVERITY | | |
| Intermittent | 15 (62) | 44 (56) |
| Persistent mild | 5 (21) | 28 (35) |
| Persistent moderate | 4 (17) | 6 (8) |
| Persistent severe | 0 | 1 (1) |
| LEVEL OF CONTROL | | |
| Controlled | 3 (12) | 20 (25) |
| Partially controlled | 19 (79) | 52 (66) |
| Uncontrolled | 2 (8) | 7 (9) |

On the basis of the data acquired and analysed the following considerations can be made:

1. The prevalence of food allergy (defined as certain if confirmed in food challenge and possible in the case of history suggestive of food allergy with associated food specific IgE levels that had a ≥95% positive predictive value for food allergy according to levels identified by Sampson [17]) in asthmatic children aged 7-19 years (mean age: 7 years) was 23% (24 cases);
2. The prevalence of food sensitization was 77% (97/103 sera available);
3. The main symptom of food allergy in a population of asthmatic children was oral allergy syndrome;

4. No correlation was found between presence of food allergy and asthma severity, but only with the level of control of respiratory disease (Table 5; Fig. 1);
5. A correlation was found between food sensitization and grade of severity and control of asthma (Table 6; Fig. 2).

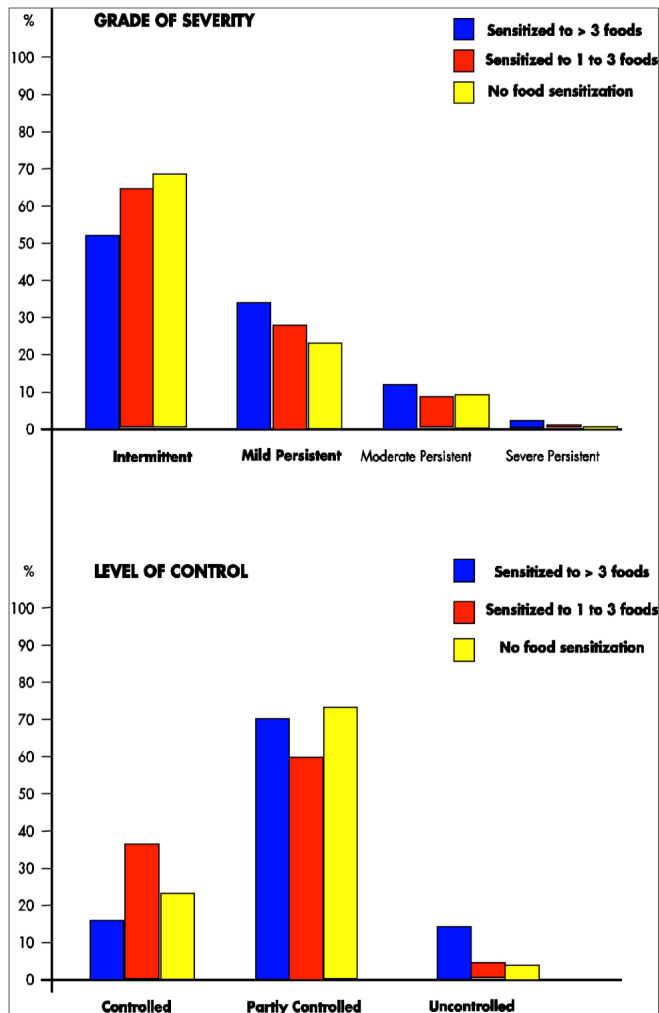


Fig. (2). Correlation between sensitization to food allergens and severity and control of asthma in 97 asthmatic children.

This study confirms the presence a higher prevalence of food allergy in asthmatic children (23%) than the general paediatric population (2-3%) Previous papers confirm that food allergy is highly prevalent among asthmatic patients, even though some studies show discordant data. The study by Novembre [6] (1988) shows a prevalence of food allergy in asthmatic children aged 2-8 years of 34%. The present study included subjects aged 7-19 years: in part of them, most food allergies, in particular to egg or milk, were outgrown by the age of 5 years. Other papers show a higher prevalence of food allergy in asthmatic children. Rancé [4] estimated a prevalence of food allergy in asthmatic children of 78% on the basis of history reported by parents of the children without confirmation of food challenge: the real prevalence of food allergy was not determined.

In the present study egg, hazelnut and peanut were the three most frequent foods inducing food allergy. In contrast with a previous paper [4], milk allergy was not included in

the three most frequent foods: this study included older children, who had probably already outgrown their milk allergy. The most common symptom found in 24 children with food allergy was oral allergy syndrome after the ingestion of raw plant-derived food (13/24; 62%). Of the 13 children with oral allergy syndrome, 12 suffered from pollinosis: the prevalence of pollen-related food allergy in pollinosis children (92/103) was about 13%. Previous studies confirm this data. Cudowska [18] showed that out of 14 pollinosis children (aged 4-17 years old) suffering from food allergy, 3 (21%) had oral allergy syndrome. As reported in previous papers, the prevalence of oral allergy syndrome in the adult population is higher than in children and is estimated at about 50-70% [19-22]. This difference can be explained by the association between pollen allergy duration and oral allergy syndrome, as the study by Asero *et al.* confirms [23]: the patients included in the present study were too young to present a higher prevalence of oral allergy syndrome. In contrast, food-induced asthma was not a common symptom in asthmatic children with food allergy: of 24 children with food allergy only 6 (29%) reported wheezing after food ingestion.

A higher rate of children with controlled symptoms was found in children without food allergy, compared with children with food allergy (25% vs 12%), but no association was found with the grade of asthma severity. The study by Roberts *et al.* [10] had shown that out of children aged 1 to 16 years ventilated for life-threatening asthma, 10 (53%) also suffered from food allergy and out of 38 children suffering from mild asthma enrolled as controls, 4 (11%) suffered from food allergy: out of the total of 57 children enrolled, 14 (25%) were affected by food allergy. This rate is similar to the rate found in the present study: this data seems to suggest that even if food allergy has a higher prevalence in asthmatic population, a correlation with severity can be found only by comparing mild cases with cases suffering from severe, life threatening asthma. In the present study too few patients suffered from severe asthma: more than half (58%) of the children recruited suffered from intermittent asthma and only 11% from moderate or severe asthma.

Moreover, a higher rate of children with persistent asthma and uncontrolled symptoms was found in those sensitized to at least 4 foods. Among subjects sensitized to at least 4 food allergens, 24 (48%) were affected by persistent asthma; among subjects sensitized to 1 to 3 foods, 9 (36%) were affected by persistent asthma; only 7 (31%) children without sensitization to any food had persistent asthma. Of the children sensitized to at least 4 allergens, 7 presented uncontrolled symptoms, compared with one child sensitized to 1 to 3 food allergens and to one nonsensitized child. Also Roberts [10] found an association between sensitization to food allergens and life-threatening asthma. Of 19 patients ventilated for life-threatening asthma, 10 (53%) were sensitized to at least one food allergen and 8 (42%) to 4 or more allergens (inhalant or food allergens). Of 38 controls with mild asthma, 5 (13%) were sensitized to at least one food and 6 (15%) were sensitized to 4 or more allergens (food or aeroallergens). Therefore Roberts indicated the presence of polysensitization in particular food sensitization as a risk factor for life threatening asthma. Julie Wang *et al.* [11], in a study on 504 sera of asthmatic children aged 4 to 9 years, similarly found a significant association between food sensi-

tization and asthma severity. Children sensitized to at least one food (milk, egg, fish, wheat, soy and peanut) presented a higher rate of hospitalization and required more steroid medications than nonsensitized patients. Julie Wang too had enrolled only children with asthma recruited from emergency departments and clinics in inner-city areas, who presented a more severe disease.

The rate of food allergen sensitization among the children enrolled in the present study was higher than in those recruited by Wang and Roberts (77% versus 45% and 26% respectively) and most children were sensitized to wheat (65; 87%), peanut (64; 85%) and soy (49; 65%). These discordant data could be explained by considering that the children in the present study were older and in more than 90% of cases suffered from pollinosis. In fact, while in the early age the sensitization to food allergens, in particular to egg and milk, can be considered a risk factor for development of respiratory allergic diseases, such as asthma or allergic rhinoconjunctivitis [24-32], in the following years of life the presence of pollinosis can determine the development of a 'pollen-related food allergy', presenting oral allergy syndrome as a clinical manifestation [19-21, 33-38].

CONCLUSIONS

This paper represents the first study in recent years which has investigated the prevalence of both food allergy and food sensitization in a population of asthmatic children. No correlation was found between presence of food allergy and asthma severity, but only with the level of control of respiratory disease: children without food allergy presented a higher rate of controlled asthma (25%) than children with food allergy (only 12%).

Moreover, children sensitized to at least four food allergens had a higher rate, though not significant (24 cases; 48%), of persistent asthma (mild, moderate or severe) than children sensitized to no more than 3 food allergens (9 cases; 36%), and than the children without any sensitization to food allergens (7 cases; 31%) and the children without food allergen sensitization or sensitized to up to 3 food allergens, presented a higher rate of controlled asthma (23% in children without food allergen sensitization and 36% in children sensitized to up to 3 food allergens) than children sensitized to at least 4 foods (only 16%).

Therefore, the presence of food allergy/sensitization should always be investigated in pollinosis children in particular if suffering from asthma. It may be interesting in a future study to widen the number of cases, to include a higher rate of subjects affected by severe asthma.

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