OPEN ACCESS Freely available online

ADVANCES IN PEDIATRIC RESEARCH

Food and respiratory allergies in children

Arnaldo Cantani [1*], Monica Micera [1]

1 Division of Allergy and Clinical Immunology, Department of Pediatrics, University of Roma "La Sapienza", Roma, Italy

Abstract

Asthma is one of the most common respiratory manifestations in children and can be provoked by food allergens through ingestion or inhalation. Clinical evidence acquired in recent years shows that the role of food in asthma is still unclear, while food allergy (FA) is regarded as one of the leading causes of atopic disease. Food allergies can result in a range of manifestations including urticaria, abdominal pain and anaphylaxis, but, above all, FA can trigger atopic dermatitis (AD). It could be that, as in AD, food allergens induce a cutaneous hyper-reactivity comparable to the bronchial hyper-reactivity (BHR) reported in allergic children with asthma. Eosinophils seem to play a major role in inducing and maintaining skin lesions, as they do in asthma. These observations suggest that the characteristic chronic AD skin lesions can be initiated, amplified and perpetuated by immunological and non-immunological factors acting in various ways and at different levels, beginning a vicious circle that results in different, but synergistic, reactions. Studies have suggested a possible link between inflammatory mediators and food-induced asthma that can be distinguished from asthma with FA. While nonspecific stimuli can contribute to triggering and worsening skin lesions, they may play a primary role in the induction of BHR. Epidemiologic studies should investigate both facets of the problem, such as asthma with FA and food-induced asthma in children. Personal data on the prevalence of respiratory symptoms in children with FA will be analyzed. We suggest that in young children food should be considered one of causes of asthma.

Citation: Cantani A, Micera M (2014) Food and respiratory allergies in children. Adv Pediatr Res 1:9. doi:10.12715/apr.2014.1.9

Received: November 17, 2014; Accepted: December 22, 2014; Published: December 31, 2014

Competing interests: The authors have declared that no competing interests exist.

* Email: acantani13@gmail.com

Introduction

Although food allergy (FA) is accepted as one of the causes of a number of atopic disorders, such as atopic dermatitis (AD), acute urticaria, vomiting, diarrhea, and systemic anaphylaxis, its role in asthma is less clear. In this paper, we briefly review the current literature on food-induced asthma and present some personal data on the prevalence of respiratory symptoms in children with FA.

Definitions and diagnosis

Correctly defining FA is a prerequisite for effective communication in scientific circles and comparison of the results of different studies. The appropriate definition of FA is mandatory to establish both the prevalence of hypersensitivity to a given food and the role of FA in asthma. There is a general agreement that FA is defined as a group of symptoms occurring locally, in the gastrointestinal tract, or in remote organs as the result of an immunological reaction. Different immunological reactions may be involved

in the clinical manifestations of FA, but the easiest immunological reaction to routinely occur is the IgE-mediated reaction. Immune complexes, as well as neutrophil chemotactic factor, have been detected in some patients with food-induced asthma following a challenge test with the relevant allergen [1, 2].

Allergen extracts currently available for skin testing to foods are not standardized, and their stability is usually poorly determined. For allergen extracts that are rapidly degraded, such as those of fruits and legumes, skin tests may be falsely negative in food-allergic patients. Conversely, some extracts may contain irritating substances, causing false positive skin tests. The titration of food-specific IgE is available only for certain foods, and in contrast with more well-characterized inhalant allergens, the sensitivity of the test is not yet known for most unpurified food allergens. Moreover, as in inhalant allergen sensitivity, the presence of food IgE in serum does not always correlate with symptoms [3].

Symptomatic hypersensitivity is present when symptoms occur during food ingestion and a specific immune response can be shown. Asymptomatic hypersensitivity exists when symptoms do not occur during food ingestion, but a specific immune response can be shown (Table 1). Double-blind placebo-controlled oral food challenge (DBPCFC) is considered the "golden standard" for the diagnosis of FA in patients enrolled in research studies or in clinical trials [4].

Table 1. Food hypersensitivity

Symptomatic	• Symptoms during food ingestion • Specific immune response • Positive challenge with the relevant food
Asymptomatic	• No symptoms during food ingestion • Specific immune response • Negative challenge with the relevant food

Epidemiology

The epidemiology of asthma triggered by FA has not been fully investigated. Several authors have examined general FA, but food-induced asthma has not been specifically studied. Even in studies that have associated food ingestion and asthma, suboptimal methodology has been used to confirm the relationship. The number of subjects with proven food-induced asthma by DBPCFC has been relatively small. Taken together, the prevalence and incidence of children with food-induced asthma has not been comprehensively and completely studied.

FA may trigger allergic respiratory symptoms through two main routes: ingestion or inhalation. Rarely, life-threatening systemic reactions, including asthma, have occurred in children with FA after inhalation of the offending food. Recently, an Italian teenager girl, allergic to cow's milk (CM), suddenly died from a severe asthma attack following milk inhalation when she entered into a dairy product factory without prior knowledge of the presence of CM [5].

It is uncommon to have respiratory symptoms as the only manifestation of FA or even respiratory combined with cutaneous and gastrointestinal symptoms [6]. According to several studies, children with asthma who are allergic to foods present some particular features. More frequently, they are children or adolescents with AD and a significantly high mean level of total serum IgE (Table 2).

Table 2. Clinical presentation of children or adolescents with food-induced asthma

High level of total serum IgE
Associated Symptoms:
Atopic dermatitis
Urticaria
Angioedema
Lip edema
Vomiting
Diarrhea
Anaphylaxis

The reason for this high IgE level is not completely known, but could be related to the presence of AD in these patients. High IgE levels, in fact, were reported in subjects with asthma with AD. Alternatively, FA may occur in patients who are "high IgE responders" and more prone to become sensitive towards many allergens, including foods. Therefore children with asthma with a history of AD and/or elevated total serum IgE level should be carefully assessed for a possible FA (Table 3) [7].

Table 3. Data to be collected in children with suspected food-induced asthma

History
Most recent symptoms
Number of symptoms
Description of symptoms
Timing of onset of symptoms
Quantity of food-eliciting symptoms
Associated symptoms

In reviewing the presentation of food-associated symptoms in 367 children with asthma, evaluated at the National Jewish Center, Bock *et al*. [6] showed that 257 children (70%) had a history of specific foods being associated with the onset of asthma symptoms. Of these 257, 163 (63%) had some symptoms produced during positive DBPCFC. Fifty-seven out of 257 children (22%) with positive DBPCFC exhibited wheezing as one of the symptoms. Five out of 257 patients (2%) had wheezing as the only symptom. In addition, 203 children underwent DBPCFC because of a history of food-associated symptoms since wheezing was not suspected of being precipitated by food ingestion. Six out of 203 children (3%) had wheezing as one of the elicited symptoms, but in 5 out of 6 children the wheezing was quite mild. None of the children had wheezing as the only symptom of a food allergic reaction [5]. To determine the prevalence of FA as a cause of exacerbation of asthma, Onorato *et al*. (7) studied 300 patients with asthma (7 months-80 years). They confirmed that asthma induced by FA has a low prevalence (2%), even in a population attending a specialty clinic. A similar prevalence has been reported by Novembre *et al*. [8], who studied 140 children with asthma. The presence of specific IgE was investigated with skin prick tests (PTC) and, in some cases, with radioallergo-sorbent tests (RAST). The patients were divided into 2 subgroups on the basis of clinical history: in 92 patients asthma was the only symptom, in 48 patients asthma was associated to other symptoms of FA. Using open food challenge tests, these authors observed symptoms related to FA in 16 out of 140 (11.4%) children. Respiratory symptoms were observed in 13 out of 140 children (9.2%), and one of these 13 had asthma as the only symptom. Moreover, 12 out of 13 children with asthma had associated symptoms (cutaneous, gastrointestinal), and 8 of out 140 (5.7%) children had immediate or delayed onset asthma [7].

The association between FA and chronic asthma has been studied by Zimmerman *et al.* [9]. These authors showed that food allergic children with asthma more often had AD, high IgE serum levels, multiple positive RAST, and chronic wheezing in comparison to non-food-allergic children. In addition, it was shown that highly atopic children (multiple positive RAST and high IgE serum level) had a significantly higher prevalence of chronic asthma. The authors conclude that highly atopic children are more prone to develop bronchial inflammation, which induces chronic persisting symptoms.

In a previous study [10] we studied 79 children from the ages of 6 months to 10 years, (median age 24 months), who fulfilled the criteria of Hanifin and Rajka [11] for the diagnosis of AD and took the challenge test. In all children, PTCs and RAST for CM protein and eggs were performed. Following 4-6 weeks of a CM- and egg-free diet, 113 open challenge tests were performed in the hospital. Nine out of 70 children had asthma during the challenge test with CM (13%). Three children out of 9 (33%) presented asthma within 2 hours following the food challenge. Specifically, 2 out the 3 children presented asthma associated with pruritus, urticaria and erythema, and 1 out of the 3 children presented with isolated asthma. None of 38 children who were challenged with eggs presented asthma following the challenge test. Moreover, 42 children (median age 20 months) with proven IgE-mediated CM allergy who visited our clinic were included in a prospective study to investigate the prevalence of CM-induced asthma (Table 4).

Table 4. Clinical features of 42 children with IgE-, cow's milk (CMA)-induced asthma with DBPCFC

	Yes	%	No	%	Total
No. of Children	11		31		42
Sex					
Male	8	73	22	71	30
Female	3	27	9	29	12
Median age (mos)	36 (10-72)		30 (10-74)		
Clinical presentation					
Atopic dermatitis	2	18	25	80	27
Atopic dermatitis + asthma*	7	64	3	10	10
Anaphylaxis	2	18	3	10	5
RAST class					
>3	4/11	36	14	45	18
<3	7/11	64	17	55	24

*p=0.0001

All children presented positive skin tests and RAST to CM proteins and immediate reactions following DBPCFC with CM. Eleven children out of 40 (27%) developed asthma 10 to 120 minutes after the challenge. Of these 11 children, 6 experienced asthma as the only symptom, and 5 presented vomiting, erythema, urticaria, angioedema and lip edema associated with asthma. In 3 out of 11 children, asthma occurred for the first time after the challenge. In addition, 5 children out of 11 even experienced asthma following the challenge with some hydrolyzed formulas (HF); in particular, in 4/5 children, asthma occurred with a partially hydrolyzed whey and for one child, with an extensively hydrolyzed casein. Interestingly, 3 out of 5 children had asthma only with a HF, which suggests that hidden allergenic epitopes may be exposed during the hydrolysis procedure.

In a study of 94 children with asthma using clinical history, PTC, RAST, and double-blind food challenge (DBFC) we have shown that food is one of the causes of asthma. Out of 94 asthmatic children, we found that 23 also had AD (24.6%). Of these, 14/23 children (8 boys and 6 girls aged 2-6 years) had positive PTC, RAST and DBFC. In all 14 patients, the main symptom after DBFC was asthma, which in 5 cases was associated with erythema, urticaria, vomiting, lip edema and angioedema. CM provoked asthma in 9 children, by partially HF in 2 children, by extensively HF in 2 children and by fish in one child. Moreover, in 3 children, asthma appeared with very small doses of CM: one drop in one case and 2 mL in two cases [12]. The respiratory reactions induced by food challenges in children with AD or pulmonary disease are completely different, but similar in their conclusion (Table 5) [13-15].

Table 5. Respiratory reactions induced by food challenges in children with pulmonary disease or atopic dermatitis

Food	Type of Disease		
	Respiratory [13]	Respiratory [14]	Atopic Dermatitis [15]
Egg	45	19*	51
Cow's Milk (CM)	19	27	28
Peanuts	6	28*	6
Wheat	5	3*	5
Soy	8	3	5
Fish	3		
Nuts	15*		

*indicates monosymptomatic children

Discussion

The relationship between FA and asthma is based on several considerations. First, inhaled food allergens may reach the respiratory tract directly. On the contrary, raw or cooked food allergens may reach the target organ after a number of steps including ingestion, digestion, uptake through the intestinal mucosa, absorption into the blood stream, etc. All of these mechanisms may significantly interfere with the immunogenicity and allergenicity of foods. Consequently, allergenic determinants may be destroyed or, conversely, hidden allergenic epitopes may be exposed. As a result, the immunogenic and allergenic potency of foods may be reduced or increased. Moreover, patients with FA may have coexisting inhalant allergies and other contributing factors aside from allergens, including pollutants, smoking, or emotions, all of which can increase bronchial reactivity (Table 6).

Table 6. Food allergy and asthma

• Does food allergy precipitate allergy?
• Does food allergy induce chronic asthma?
• What is the prevalence of food-induced asthma?
• Do crossreactions between inhalant and food allergens precipitate asthma?

Foods may also induce respiratory symptoms involving non-allergenic mechanisms. For example, substances such as egg, milk, nuts, chocolate and food additives (sulphites, benzoate, tartrazine, etc.) may cause wheezing in patients with asthma but do not elicit a reaction when ingested via oral challenge test. It has been shown that these substances may enhance airway reactivity instead of provoking airways obstruction directly [16]. Once airway reactivity is enhanced, other common triggers of asthma, such as cold air or drinks, exercise [17] or other environmental factors, could readily precipitate acute bronchoconstriction. It has been reported that non-specific airway reactivity becomes increased after DBPCFC with cold drinks but not after challenge with soda or water [18].

Conclusions

While it is clear that foods may induce FA in children, at present, there are no definitive data on the prevalence of such an association. According to our studies, children with asthma and AD, have a significantly higher prevalence of food-induced asthma. The cells, mediators, and mechanisms involved in food-induced asthma are not completely known. Moreover, crucial further investigation is warranted to determine whether airway reactivity increases following a positive challenge test with the offending food, or if it increases daily if the child is not compliant to their diet (Table 7), as a similar phenomenon has been observed in patients with asthma when they are exposed daily to the relevant inhalant allergens.

Table 7. Patterns of management of food-induced asthma

• Children with anaphylaxis accompanied by wheezing
• Children with chronic asthma on a restricted diet because parents and/or physicians claim that food(s) precipitate wheezing
• Children who improved on a restricted diet without challenging the association between foods and symptoms
• Children on a restricted diet because positive skin test and/or RAST responses to food(s)

References

1. Paganelli R, Levisky RJ, Brostoff J, Wraith DG. Immune complex containing food proteins in normal and atopic subjects after oral challenge and effect of sodium cromoglycate on antigen absorption. Lancet. 1979;16;1270-2.
2. Papageorgiou N, Lee TH, Nagakura T, Cromwell 0, Wraith DG, Kay AS. Neutrophil chemotactic activity in milk-induced asthma. J Allergy Clin Immunol. 1983;72:75-82.
3. Giampietro PG, Ragno V, Daniele S, Cantani A, Ferrara M, Businco L. Soy hypersensitivity in children with food allergy. Ann Allergy. 1992;69;143-6.
4. Cantani A. Pediatric asthma before treated should be prevented. Eur Rev Med Pharmacol Sci. 1999;3:237-8.
5. Vargiu A, Vargiu G, Locci F, Del Giacco S, Del Giacco GS. Hypersensitivity reactions from inhalation of milk proteins. Allergy. 1994;49;386-7.
6. Bock SA. Food hypersensitivity and asthma in children. In: Tinkelman DG, Naspitz CK. Childhood asthma. Pathophysiology and treatment. New York: Marcel Dekker, Inc, 1993, pp 537-51.
7. Onorato J, Merland N, Terral C, Michel FB, Bousquet J. Placebo-controlled double-blind food challenge in asthma. J Allergy Clin Immunol. 1986; 78;1139-46.
8. Novembre E, De Martino M, Vierucci A. Foods and respiratory allergy. Allergy Clin Immunol. 1988;81:1059-65.
9. Zimmerman B, Chambers C, Forsyth S. Allergy i4 asthma II. The highly atopic infant and chronic asthma. J Allergy Clin Immunol. 1988;81:71-7.
10. Meglio P, Giampietro PG, Farinella F, Cantani A, Businco L. Personal experience in the diagnostic procedures in children with atopic dermatitis and food allergy. Allergy. 1989;S9:165-73.
11. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Dermatol Venereol (Suppl). 1980;92:44-7.

12. Cantani A, Gagliesi D. Food allergens provoke asthma in children. ERS Annual Congress, Geneva, September 19-23, 1998. Eur Respir J. 1998;12:S443.
13. James JM, Eggleston PA, Sampson HA. Airway reactivity changes in food-allergic, asthmatic children undergoing double-blind, placebo-controlled food challenges. Am J Respir Crit Care Med. 1994;149:59-64.
14. Bock SA. Respiratory reactions induced by food challenges in children with pulmonary disease. Pediatr Allergy Immunol. 1992;3:188-98.
15. Sampson HA, James JM. Respiratory reactions induced by food challenges in children with atopic dermatitis. Pediatr Allergy Immunol. 1992;3:195-200.
16. Bahna S. Food allergy and the respiratory tract. Allergie immunol. 1991;23:384-6.
17. Kidd JM, Cohen SH, Sosman AJ. Food-dependent exercise-induced anaphylaxis. J Allergy Clin Immunol. 1980;71:407-11.
18. Wilson N, Vickers H, Taylor G, Silverman M. objective test for food sensitivity in asthmatic children: increased bronchial reactivity after cola drinks. BMJ. 1982;284:1226-68.