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## FOOD ALLERGENS AND RESPIRATORY SYMPTOMS

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Food allergy may be clinically expressed by a variety of respiratory symptoms, which can be provoked either by IgE- or cellular mediated reactions. Among the diagnostic procedures, newly introduced atopy patch test seems to be important for diagnosis of cellular, delayed immune reactions. We studied the prevalence of positive atopy patch tests with food and inhalant allergens and the correlation between the positivity of atopy patch tests and questionnaire derived atopic and non-atopic respiratory symptoms and diseases in an unselected children population. We found a correlation between the positive patch test result with wheat and cough after physical effort, allergic rhino-conjunctivitis, and bronchitis recidivans. The subjects with positive skin reaction to egg suffered from allergic rhino-conjunctivitis and bronchial asthma. Food and inhalant allergens play an important role in the induction and exacerbation of some respiratory allergic diseases. The positive correlation of positive results of skin tests and history of some respiratory diseases and symptoms also on the population level confirm the importance of these tests in the diagnostic work-up of these allergic diseases.

**Key words:** *atopy patch test, children, food allergens, questionnaires, respiratory disease*

## INTRODUCTION

Food hypersensitivity (FH) affects nearly everyone at same point, either as an unpleasant reaction to something eaten or as a concern for a family member suspected of having food allergy (FA). Increasing public and medical interest have also popularized claims that a variety of physical and psychological symptoms are

the result of food hypersensitivity. The ratio of perceived FH in the general population is about 25%. However, the prevalence of true food allergy is approximately 8% in children under 1 year, 2-3% in children between 1-3 years and about 1-2% in adults (1). Therefore, it is very important to determine if the food really causes these symptoms or if there are other underlying factors. According to the revised classification of allergic diseases (2), food hypersensitivity can be divided into two groups: immunologically-mediated reactions (food allergy) and non-immunologically-mediated reaction (food intolerance). According to the involved immune mechanism, food allergy can be divided into IgE-mediated (reaction type-I), non-IgE-mediated (cellular FA, reaction type III or IV), and combined (mixed IgE- and non-IgE-mediated) reactions. Non-IgE mediated food allergy is supposed to be a cell-mediated immunologic reaction, which involves immune complex formation and complement deposition. Non-IgE-mediated food sensitivities are becoming increasingly recognized. This group is represented by a spectrum of clinical diseases attributed to adverse immune responses to food, for which IgE antibodies to the causal food can not be demonstrated, at least not by routine tests. The onset of these reactions is slower than immediate IgE-mediated reactions, ranging from a few hours to more than a week after the ingestion of the causative agent. In some cases, even more prolonged and repeated exposure is required for the development of clinically apparent abnormalities. Most of the diagnosis is made on the basis of clinical presentation and responses to dietary exclusion (dechallenge) (1).

Food allergy is more common in children than in adults and, as a target organ, the respiratory tract is probably next in frequency to the gastrointestinal tract and skin. In addition, respiratory obstruction is often a major component of food-triggered systemic anaphylaxis. Respiratory symptoms can occur not only as a reaction to the food proteins, but also can be provoked by various additives and chemicals contained in the ingested food (3). The role of food in causing respiratory allergies is probably underestimated. Food-induced upper respiratory tract symptoms seem to be more common in infants and young children, but are probably markedly misdiagnosed (*Table 1*). Allergic rhino-conjunctivitis is characterized by periocular pruritus, tearing and conjunctival erythema, nasal congestion, rhinorrhea, and sneezing shortly after ingestion of causal food. Chronic serous otitis media may develop secondary to chronic rhinitis and Eustachian tube dysfunction, or the middle ear itself can be primary involved organ. Food-induced asthma is more common in young children, particularly in association with atopic eczema. The role of FA can be subclinical, i.e., causing bronchial hyperreactivity without clinical symptoms. Approximately in every fifth asthmatic the possible role of FA should be taken into account. Food-induced asthmatic reactions should be suspected in patients with refractory asthma and a history of atopic eczema, gastroesophageal reflux, food allergy or feeding problems as an infant, or a history of positive skin test results or reactions to a food. Vapors and steam emitted from cooking food (e.g., fish) can induce asthmatic reactions (4). The Heiner syndrome is a chronic pulmonary disease

Table 1. Respiratory manifestations of food allergy.

| <b>IgE-mediated<br/>Acute respiratory symptoms</b> | <b>Non-IgE-mediated<br/>Chronic respiratory symptoms</b>                  |
|----------------------------------------------------|---------------------------------------------------------------------------|
| Allergic rhino-conjunctivitis                      | Hypersensitivity pneumonitis                                              |
| Laryngeal oedema                                   | Pulmonary hemosiderosis associated<br>With food allergy (Heiner syndrome) |
| Atopic asthma                                      | Non-atopic asthma                                                         |
| Bronchial hyperreactivity                          | Chronic otitis media with effusion                                        |
| Systemic anaphylaxis                               |                                                                           |
| Food-associated exercise-<br>induced anaphylaxis   |                                                                           |

caused by food hypersensitivity, particularly to cow milk proteins during infancy. The predominantly involved immune mechanisms are cellular immunity and immune-complex formation. It is characterized by recurrent pneumonia, pulmonary infiltrates, iron deficiency anaemia, and a failure to thrive in small children (4). If the vasculitis is severe, alveolar bleeding occurs and causes pulmonary haemosiderosis. Hypersensitivity pneumonitis to inhaled soy-bean flour has been described (5). Generalized anaphylaxis as a result of food allergy accounts for at least a third of all patients with anaphylaxis seen in hospital emergency departments. In addition to variable expression of cutaneous, respiratory, and gastrointestinal symptoms, patients may have cardiovascular symptoms, such as hypotension, vascular collapse, and cardiac dysrhythmias. Food-associated exercise-induced anaphylaxis is an unusual form of anaphylaxis that occurs only when the patient exercises within 2 to 4 hours after ingesting a food, whereas in the absence of exercise, the patient can ingest the food without any apparent reaction. It is most common in women 15 to 35 years old (6). Gustatory rhinitis is caused by a neurogenic reflex in persons who experience profuse watery rhinorrhea while eating, particularly spicy foods (5).

Food allergy represents one of the most important problems of pediatric allergology and immunology. Diagnosing of FA is very challenging and not as easy as it seems at first sight. In the correct diagnosis of FA, close cooperation among immunologists, allergologist, gastroenterologist, dermatologist, pneumologist, and pediatricians is necessary. As in other diseases, the allergy diagnosis is established in several steps, with detailed analysis of personal and family history, and a careful physical examination to start with. Diet diaries are used as an adjunct to history over a specified time period and may help to reveal unknown sources of food allergens. Skin prick test (SPT) with native foods (so-called prick-by-prick technique) may be more reliable than SPT with commercially extracts in screening patients with suspected IgE-mediated FA. While negative SPT, according to some authors, nearly exclude IgE-mediated allergy, positive tests do not prove relevant allergy. In few studies, food-specific IgE to food allergens showed good correlation with

provocation test results. Specific elimination diets should be initiated before oral exposition test, which remains "the gold standard" in the diagnosis of FA. Preferably, the provocation is performed as double-blind placebo controlled food challenge, *e.g.*, with masked (lyophilized) foods in colored and flavored neutral formulas after at least 2 weeks of corresponding elimination diet (1).

A simple, inexpensive, and reliable test for food allergy has been sought by food allergists for decades. Recently, the atopy patch test (APT) has been introduced into clinical use. APT (atopy patch test, atopic patch test, skin patch test, epicutaneous patch test, allergen patch test, allergic patch test, cutaneous contact test) has left experimental grounds and is increasingly used as a standard diagnostic procedure for characterizing patients with aeroallergen- and food-triggered disorders. The test procedure of APT is very similar to the classic patch test; it differs in the nature of allergens used. These are not, as in classic patch test, haptens, but intact protein allergens that are frequently used for SPT to demonstrate and IgE-mediated type I sensitization. Hence, the APT is not only a delayed-type hypersensitivity reaction as initiated in tuberculosis skin test (7). In the APT, we suppose the predominance of cellular-mediated reaction with evident participation of other immunological mechanisms (IgE, IgG, circulating immunocomplexes, complement, *etc.*). The APT has been used as a model for early AD lesions and is performed like a normal patch test with haptens, but with protein allergens. The atopy patch test could be defined as an epicutaneous test known to elicit IgE-mediated reactions, in which the test sites are evaluated for an eczematous reaction after 48 to 72 h (8). Primarily, the APTs were studied for aeroallergens, but several years ago, the APT with food allergens has been introduced into clinical practice.

## MATERIAL AND METHODS

The study was approved by the Ethical Committee of the Pediatric Clinic of Rome University 'La Sapienza' in Italy. Informed statement was achieved and signed by the parents of all tested children.

We studied an unselected population of 532 children (50.6% boys, 49.4% girls) attending three elementary schools in the north of Rome in Italy from October 2005 to March 2006. The mean age of the subjects was  $10.2 \pm 2.3$  years. For 1 week before skin testing, all children were asked to refrain from antihistamine medications and from inhaled or oral corticosteroids. All the children or their parents fulfilled standardized questionnaires aimed in detection of atopic and non-atopic respiratory symptoms and disorders in the last year and in the past personal history: nocturnal cough, cough after physical effort, nasal obturation and/or secretion, bronchitis, pneumonia, otitis media, allergic rhino-conjunctivitis, laryngitis, and bronchial asthma.

### *Atopy patch test (APT)*

Atopy patch tests were done with plastic quadratic chambers 10 mm in diameter (Finn Chambers, Haye's, the Netherlands). The allergens (1 drop, 50  $\mu$ l) were placed into the chambers and were attached to an area of unaffected skin on the children's backs on both sides. As a negative control, physiological solution was used. For the allergens we used four fresh foods: cow milk (containing 3.5% fat), whisked hen egg (white and yolk), tomato, and wheat flour (dissolved in saline, 1g/10 ml). The occlusion time

was 48 h. The results were read out 20 min after removing the chambers and then after 72 h for the final test evaluation. APT was repeated after a certain period of time: in the first group after 7 days, in the second group after 14 days, and finally, in the third group after 21 days. The criteria of a read out were recommended by the revised European Task Force on Atopic Dermatitis 'Key for Atopy Patch Test Reading' (7). Positive reaction were classified using [+] for erythema and infiltration, [++] for erythema and fewer than 3 papules, [+++] for erythema and four or more, or spreading papules and [++++] for erythema, papules, and vesicles. Reactions were classified as positive if the test yielded erythema with infiltration, papules, or both. Erythema without palpable infiltration was considered questionable. In the final evaluation, questionable results were considered negative. As a negative control, we used a solution of physiological saline in all tested children, except the four tested food allergens. All the test results were read out by the same well-trained operator (immunoallergologist).

### Statistical methods

Data were analyzed with the software package SPSS version 9.0 (SPSS Inc. Chicago, IL, USA). Student's two-tailed *t* test, chi square ( $\chi^2$ ) test and Fisher's exact test were used for statistical comparison.  $P \leq 0.05$  was considered to indicate statistical significance.

## RESULTS

In our unselected population of 532 schoolchildren, we studied a correlation between several questionnaire-derived data and positive results of atopy patch tests with food and inhalant allergens. The calculated frequencies of selected

*Table 2.* Questionnaire-derived frequencies of atopic and non-atopic respiratory symptoms or diseases in an unselected population of school children.

|                                                          | Incidence<br>in the last year |                |                | Incidence<br>in the past history |                |                |
|----------------------------------------------------------|-------------------------------|----------------|----------------|----------------------------------|----------------|----------------|
|                                                          | <i>Never</i>                  | <i>Rarely</i>  | <i>Often</i>   | <i>Never</i>                     | <i>Rarely</i>  | <i>Often</i>   |
| Nocturnal cough                                          | 198/497<br>(39.8%)            | 262<br>(52.7%) | 37<br>(7.4%)   | 124/447<br>(27.7%)               | 248<br>(55.5%) | 75<br>(16.8%)  |
| Cough after<br>physical effort                           | 384/495<br>(77.6%)            | 84<br>(17.0%)  | 27<br>(5.5%)   | 340/447<br>(76.1%)               | 72<br>(16.1%)  | 35<br>(7.8%)   |
| Nasal obturation<br>or secretion                         | 107/506<br>(21.1%)            | 284<br>(56.1%) | 115<br>(22.7%) | 74/461<br>(16.1%)                | 250<br>(54.2%) | 137<br>(29.7%) |
| Bronchitis                                               | 355/488<br>(72.7%)            | 119<br>(24.4%) | 14<br>(2.9%)   | 186/421<br>(44.2%)               | 172<br>(40.9%) | 63<br>(15.0%)  |
| Pneumonia                                                | 461/479<br>(96.5%)            | 16<br>(3.3%)   | 1<br>(0.2%)    | 360/409<br>(88.0%)               | 39<br>(9.5%)   | 10<br>(2.4%)   |
| Otitis media                                             | 333/482<br>(69.1%)            | 115<br>(23.9%) | 34<br>(7.1%)   | 167/423<br>(39.5%)               | 152<br>(35.9%) | 104<br>(24.6%) |
| Allergic rhino-<br>conjunctivitis                        | 399/491<br>(81.3%)            | 50<br>(10.2%)  | 42<br>(8.6%)   | 326/418<br>(78.0%)               | 44<br>(10.5%)  | 48<br>(11.5%)  |
| Laryngitis                                               | 363/482<br>(75.3%)            | 86<br>(17.8%)  | 33<br>(6.8%)   | 255/414<br>(61.6%)               | 101<br>(24.4%) | 58<br>(14.0%)  |
| Bronchial asthma (dyspnea,<br>chest tightness, wheezing) | 440/484<br>(90.9%)            | 27<br>(5.6%)   | 17<br>(3.5%)   | 347/419<br>(82.8%)               | 31<br>(7.4%)   | 41<br>(9.8%)   |

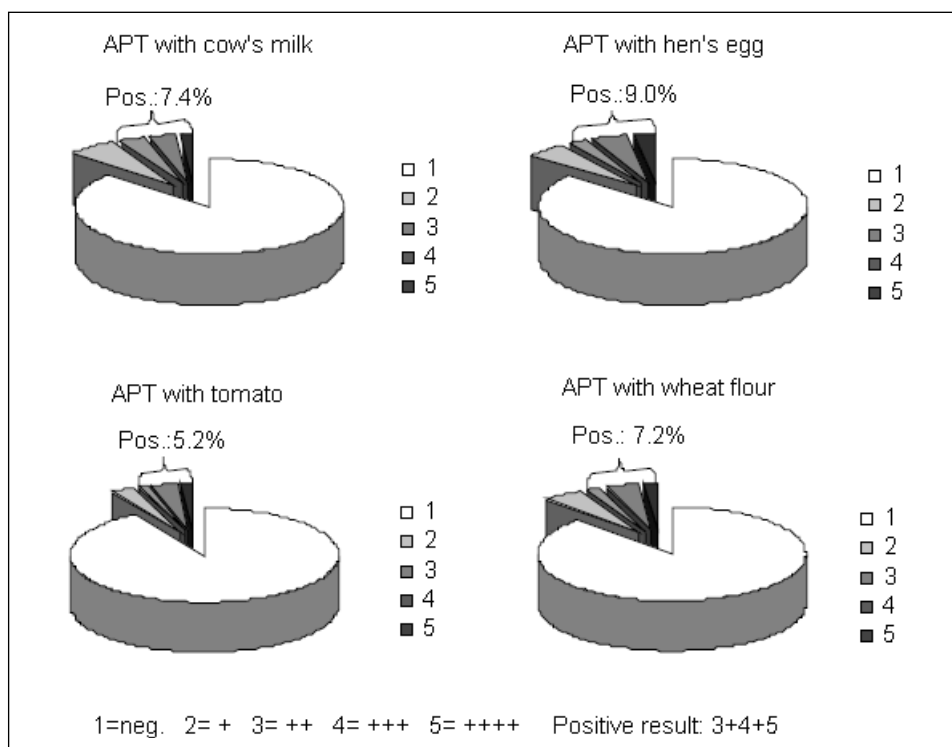


Fig. 1. Frequency of positive APT reaction with fresh food allergens in an unselected population of Italian school children.

atopic and non-atopic respiratory symptoms and diseases (nocturnal cough, cough after physical effort, nasal obturation, bronchitis, pneumonia, otitis media, allergic rhino-conjunctivitis, laryngitis, and bronchial asthma) are reported in the *Table 2*.

In our unselected population of Italian schoolchildren, we observed in 7.4% positive APT results with cow milk (frequency of strong positive reactions with papules was 4.7%), and in 9.0% positive APT with hen egg (strong positivity in 7.0% of children). 5.2% children showed positive results with tomato (4.4% strong positive reactions) and 7.2% with wheat flour (5.6% strong positive reactions) (*Fig. 1*). Two inhalant allergens yielded positive results in 29.8% (*Dermatophagoides pteronyssinus*) and 3.8% (mixed grasses) of studied children.

We analyzed the association between the positivity of APT with four fresh food allergens (cow milk, hen egg, wheat flour, and tomato) and two inhalant allergens (*Dermatophagoides pteronyssinus* and mixed grasses) and questionnaire-derived incidences of atopic and non-atopic symptoms and disorders in the last year and in the past personal history: nocturnal cough, cough after physical effort, nasal obturation and/or secretion, bronchitis, pneumonia, otitis media, allergic rhino-conjunctivitis, laryngitis, and bronchial asthma. The

children with positive APT to wheat flour had more frequent cough after physical effort in the past ( $P=0.033$ ) or in the last year ( $P=0.019$ ). Children with positivity to wheat flour more frequently suffered from allergic rhino-conjunctivitis ( $P=0.031$ ) in the last year. They also had frequently bronchitis recidivans in the past ( $P=0.019$ ). The subjects with positive APT reactions to hen egg suffered from allergic rhino-conjunctivitis in the past ( $P=0.020$ ) or in the last year ( $P=0.050$ ) compared with those with negative results of the APT with hen egg. These children also had bronchial asthma in the past ( $P=0.028$ ). In children with positive APT with mixed grasses, we observed a higher prevalence of bronchial asthma in the past ( $P=0.011$ ) in comparison with children with negative APT results. In children with anamnestic data on the other respiratory symptoms (nocturnal cough, nasal obturation, and/or secretion) or diseases (pneumonia, otitis media, and laryngitis), we were not able to detect the association with positive APT results either with food allergens or aeroallergens.

#### DISCUSSION

The first finding from our large epidemiological study on the APT in unselected population of Italian school children is that this diagnostic procedure produces positive reactions for inhalant and food allergens in a significant number of subjects in the general population. Of note is the observed correlation between the positivity of APT with particular allergens and some questionnaire-derived respiratory atopic or non-atopic symptoms and diseases. This finding contradicts some reported statements that APT seems to be specific for sensitized patients with atopic dermatitis, and do not occur in healthy volunteers or in patients suffering from asthma or rhinitis (9). In the study of Vanto *et al* (10) infants with AD did not have positive patch test reactions to cow milk more often than those without atopic eczema (15% and 10%, respectively). Positive responses in APT with aeroallergens do not occur more often in patients with atopic dermatitis, although atopy is correlated with increased skin irritability. Therefore, the APT does not appear to be suitable to distinguish subgroups of patients characterized by atopic dermatitis, asthma, or allergic rhinitis (11). It has been also shown that healthy controls and patients with respiratory atopy without the history of eczema do not react to the APT (12, 8) or respond with a lower frequency and intensity of APT reactions (13). As no gold standard for aeroallergen provocation in AD exists, the relevance of aeroallergens for AD flares may be evaluated by APT in addition to SPT and sIgE. Whitmore *et al* (14) studied the prevalence of positive APT with aeroallergens in subgroups of patients with AD and/or mucosal atopy. The prevalence of reactions in patients with both atopic dermatitis and mucosal allergy (18.8%) was significantly greater than the prevalence (2.3%) in patients with only one or neither of these two atopic disorders ( $P=0.02$ ). It has been suggested that APT works only in the patients with

atopic dermatitis (14, 15). In the study of Keskin *et al* (16), the authors observed isolated skin symptoms of FA only in 4 patients, the other with positive APT with cow milk had various combinations of symptoms from the part of gastrointestinal, respiratory, skin system, or had systemic anaphylactic reaction. This suggests that APT may be also useful for infants who have allergic manifestations other than AD. The APT positivity is not specific for the patients with AD, since many studies have observed also positive results in the groups of patients with, *e.g.*, gastrointestinal food allergy or respiratory allergy without skin involvement (17). Food patch test shows good diagnostic accuracy not only for the skin manifestation of FA, but also for the signs in other organs or systems (gastrointestinal, CNS, articular, and respiratory). APTs have been found to be positive also among the children with FA with gastrointestinal or respiratory symptoms without skin involvement (10, 18, 19).

While dermatologic, respiratory, and systemic manifestations of FA are well recognized, reactions manifesting primarily in the digestive tract can be difficult to recognize, diagnose, and treat (4, 20). Food allergy is now being increasingly recognized in conditions previously not labeled as 'allergic', such as gastroesophageal reflux disease (20). Non-recognition of FA may lead to inappropriate treatment and to confusion with primary gastroesophageal reflux with potentially hazardous decisions (*e.g.*, surgery) (21). APT is useful method in detection of food allergy in children with isolated digestive symptoms without AD (18). Twenty four patients with diagnosed cow milk allergy (CMA) without AD were tested. APT with cow milk was positive in 79% children with CMA with gastrointestinal symptoms. Good SE and SP for the APT with CM have been observed in the patients with CMA and isolated gastrointestinal symptoms. A large use of APT in the presence of isolated digestive symptoms could improve detection of conditions related to CMA. Therefore, a fast standardization of this testing procedure seems to be mandatory. In several studies it has been shown that APT with food allergens is useful also in the diagnostic work-up of food protein-induced enterocolitis syndrome which is characterized by profuse vomiting and/or diarrhoea several hours after ingestion of particular food (usually the most involved foods are cow and soy milk, but also poultry, peas, fish, cereals, lentil, sweet potato, and bean) (18, 19). APT can be used as a sensitive diagnostic tool also in eosinophilic esophagitis (22, 23). Eosinophilic esophagitis is a recently described disorder identified in patients with symptoms suggestive of gastroesophageal reflux disease but unresponsive to conventional reflux treatment and have normal pH probe results (23, 24).

Guler *et al* (25) performed APT and SPT in 63 children suffering from asthma or allergic rhinitis. All the patients had positive SPT and high serum specific IgE levels for *Dermatophagoides pteronyssinus*. APT was performed with *Dermatophagoides* in petrolatum (200 IR/ml). Of the 63 patients, 25% showed a positive APT result. APT testing may partly identify mite sensitive children with respiratory allergy. Positive APT results may imply that delayed hypersensitivity

reactions play a role in children with asthma or allergic rhinitis. In patients with respiratory allergy, the positive APT results were less frequent suggesting that the involvement of delayed hypersensitivity in respiratory allergies is less important than in atopic dermatitis.

It is evident that food and inhalant allergens play important role in the induction and exacerbation of some respiratory allergic diseases. The observed correlation of positive results of atopy patch tests with food and inhalant allergens and history of some respiratory diseases and symptoms also on the population level confirms the importance of this skin test in the diagnostic work-up also of respiratory allergic diseases.

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