Effects of food allergens on asthma exacerbations in schoolchildren with atopic asthma

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ABSTRACT
Although the prevalence with which food causes asthma is not well known, food allergy is implicated in a variety of respiratory symptoms. Eighty-two asthmatic children aged 6–16 years with doctor-diagnosed sensitization to inhalants and presenting with asthma exacerbation participated in this study of food allergies linked to asthma exacerbations. The diagnosis of food allergy was established using a questionnaire, clinical criteria, serum-specific IgE antibody measurements, and an atopy patch test. Asthma exacerbation was determined using fractional exhaled nitric oxide management after the children were admitted to the hospital. On the basis of questionnaire data, suspected food allergy was identified in 59.8% children. The positive and negative rates of serum food-specific IgE tests were 54.9% and 45.1%, respectively. The results of atopy patch tests in radioallergosorbent-positive participants were 88.9% positive and 12.5% negative. Food allergy is a risk factor for asthma exacerbation, and evaluation of food allergy in selected patients with asthma is indicated.

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Introduction
Eczema and food allergen sensitization are risk factors for the development of asthma, and the relationship of these atopic conditions is frequently referred to as the atopic match (Ker & Hartert, 2009). Food allergy and asthma frequently co-exist, but the true prevalence is difficult to ascertain. Children with food allergy are more than two to four times as likely to have other atopic conditions such as asthma, eczema, or respiratory allergy compared to children without food allergies (Branum & Lukas, 2008). Friedlander et al. (2013) found an increased risk of asthma morbidity in children with any food allergy, and even greater morbidity was found in children with multiple food allergies. Independent of markers of atopy such as aeroallergen sensitization and family history of asthma, a significant association exists between food allergy and asthma. This association is even stronger in subjects with severe food allergy (Schroeder et al., 2009). Although food allergens are a rare trigger of food-induced asthmatic reactions in schoolchildren with asthma, they can enhance bronchial hyperreactivity despite a lack of evident clinical respiratory signs.

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and a decrease in forced expiratory volume in 1 s values after food challenge (Krogulska et al., 2016). The prevalence of asthma induced by food allergy is low. Rance and Dutau studied asthma induced by food allergy in 9.5% of their group of children who underwent food challenges but identified asthma alone in only 2.8% of the children. In another study, food allergy related to immunoglobulin E (IgE) was present in 9.8% of children with asthma. In children with asthma, the prevalence of respiratory manifestations induced by foods is 4.1% (Krogulska, Wąsowska-Królikowska, & Dynowski, 2007).

Children with food-induced asthma exacerbations demonstrated significantly greater severity, poor control, and worse morbidity compared to those without such exacerbations (Krogulska, Dynowski, Funkowicz, Małachowska, & Wąsowska-Królikowska, 2015). In children with asthma, the risk of being hospitalized is greater if the patients are allergic to food, especially in those with food-induced respiratory reactions (Friedlander et al., 2013; Simpson, Glutting, & Yousef, 2007; Simpson, Yousef, & Hossain, 2010). Further, asthma and bronchial hyper-responsiveness are observed significantly more often in patients with specific serum IgE to food allergens (Cuesta-Herranz et al., 2010). Patients with asthma are five times more likely to report adverse reactions to food than are members of the general population (Longo, Berti, Burks, Krauss, & Barbi, 2013; Ozol & Mete, 2008). Experts estimate that 2–73% of asthmatic patients may be affected by food-induced exacerbations (Krogulska et al., 2015, 2016; Krogulska, Dynowski, & Wąsowska-Królikowska, 2010). However, it is not clear from these studies whether asthma exacerbations were triggered by exposure to the food allergen, but evaluation of food allergy in patients with asthma is indicated. Accordingly, this study reports the results of our evaluation of food allergy in a group of children with atopic asthma.

**Materials and methods**

Eighty-two schoolchildren with physician-diagnosed atopic asthma and identified between February 2015 and March 2016 were enrolled in the study. All were patients of the Department of Pediatric Allergy, Immunology and Rheumatology, Taipei City Hospital, Renai Branch, and West Garden Hospital, Taipei City, Taiwan. The parents of all patients provided written informed consent, and the study protocol was approved by the ethics committee of Taipei City Hospital and West Garden Hospital.

Inclusion criteria were as follows: age between 6 and 16 years, the presence of atopic asthma diagnosed according to the Global Initiative for Asthma (GINA) criteria (www.ginasthma.org), and the ability to cooperate while investigators performed the fractional exhaled nitric oxide (FeNO) examination. Asthma was diagnosed on the basis of symptoms, the results of the physical examination of the respiratory system, and the presence of FeNO levels that were higher than 20 ppb. Exclusion criteria were as follows: the presence of diseases other than food allergy that could increase the risk of asthma exacerbation or influence the study procedures, or use of a systemic steroid within 2 weeks of the study. Patients with atopic asthma were evaluated for food allergy by means of a questionnaire and the results of an inhalants- and food-specific IgE test (ImmunoCAP-FEIA; Thermo-Fisher Scientific, Taipei, Taiwan). The common food allergens, which we evaluated including crab, shrimp, lobster, clam, squid, tuna, salmon, blue mussel, octopus, cow milk, goat milk, soybean, egg white, egg yolk, cheese, wheat, peanut, garlic, pork, beef, chicken, banana, pine apple, peach, mango, kiwi, and melon. The inhalant-specific IgE, which
we analyzed containing Dermaophagoides pteronyssinus, Dermatophagoides farinae, Blomia tropicalis, candida, cat dander, dog dander, ragweed and German cockroach. The food-specific atopic patch test (FAPT) is followed with European Academy of Allergy and Clinical Immunology/Global Allergy and Asthma European Network in 2006. The FAPT use an epicutaneous patch technique to occulsively apply food natural antigens to the skin to induce inflammatory reaction at the patch application site; the evaluation of the test reaction is done after 48 and 72 h using the European Task Force on Atopic Dermatitis (ETFAD) reading key. The positive predictive values increased with the appearance of indurations and number of papules. The true positive FAPT rate increased from scores of 1+ to 3+. Food-specific atopic asthma patch tests were administered to serum food-specific IgE test-positive patients. The performance characteristics of the ImmunoCAP-FEIA test were compared with those of atopic asthma patch tests. Pearson’s $\chi^2$ test was used for all statistical analyses. Statistical significance set at $p < .05$.

Results

Familial atopic asthma was found in 75 children (91.5%). All the participants completed and returned the questionnaire. The most sensitive and specific questions in identifying asthmatic children by the questionnaire was question asking about diagnosis (has the child ever had food-induced asthma?) rather than those covering asthma symptoms such as wheeze, shortness of breath, and/or cough. Inhalant sensitization was documented in all participants and showed that the positive rates to mite, German cockroach, cat dander, dog dander, mold, and ragweed were 92%, 34%, 24%, 18%, 17%, and 2%, respectively. The most common food-mediated respiratory symptoms after ingestion in the answers of questionnaire were seafood (crab, shrimp lobster, clam, and squid). The mean total FeNO concentration among the 82 schoolchildren was 33.9 ppb, which showed the state of asthma exacerbation identified with physical examination of each participant. The positive results of the serum food-specific IgE test (54.9%, $n = 45$) were comparable with those of the food allergen atopy patch test (88.9%, $n = 40$), and the data from the questionnaire confirmed suspicions of food allergy (59.8%, $n = 49$). However, there was no statistical significance found in the relation between asthma exacerbation/coughing and food allergy (Pearson’s $\chi^2$ test, $p = .93$).

Discussion

Subclinical inflammation in gut mucosa has been demonstrated in bronchial asthma, suggesting that the whole mucosal system is involved in allergic diseases 3 (Krogulska et al., 2010). Previous studies have shown a 10-fold discrepancy in self-reported food-induced symptoms and physician-diagnosed food hypersensitivity. Severe food allergy was observed in individuals with pre-existing atopic disease, and these patients should be fully investigated for clinically relevant food allergy 4 (Soost et al., 2009). Food allergy is frequently underestimated in association with asthma, but food allergy has been shown to trigger or exacerbate bronchial obstruction in 2–8.5% of children with asthma. Also, food allergy more often occurred in children with asthma and concomitant skin and gastrointestinal disorders than in those who presented only with asthma. Therefore, a diagnosis of possible concomitant food allergy should be considered in children
with asthma 5 (Celik-Bilgili et al., 2005). Because the ImmunoCAP-FEIA provides a quantitative assessment of allergy-specific IgE antibody, the present study was undertaken to determine the potential utility of this test in the diagnosis of IgE-mediated food hypersensitivity. The findings could eliminate the need to perform double-blind, placebo-controlled food challenges in a significant number of patients suspected of having IgE-mediated food allergy 6 (Beausoleil, Fiedler, & Spergel, 2007). The atopy patch test has recently been introduced into the diagnostic work-up for food allergy. This test, together with the determination of specific IgE levels, reduces the need for oral food challenges in children 7 (Beausoleil et al., 2007; Mehl et al., 2005).

Like other studies that reported that 34–78% of asthmatic patients have food-related symptoms, our findings indicate that more than half of the atopic asthma children in our study reported food-related complaints. The onset of asthma exacerbation in the schoolchildren usually occurred within minutes to 2 h of food ingestion. Each patient’s asthma exacerbation was confirmed by elevation of FeNO levels greater than 20 ppb (mean, 33.9 ppb). Moreover, the positive rate of serum food-specific IgE test in the schoolchildren was 54% (n = 45), and among them the food allergen atopy patch test was positive in 88.9% (n = 40). According to this study, the foods most commonly associated with patient complaints were crab (67.9%), cow’s milk (53.6%), shrimp (50%), lobster (46.9%), egg white (46.5%), garlic (46.3%), clam (32.1%), squid (28.9%), goat’s milk (25%), octopus (21.4%), kiwi (21.2%), wheat (17.8%), and peanut (14.3%).

In conclusion, food allergy may be an important risk factor for asthma exacerbation among schoolchildren with atopic asthma, and a combination of an antigen-specific IgE test and atopy patch test can reduce the need to conduct double-blind, placebo-controlled food studies in a significant number of patients suspected of having IgE-mediated food allergy.

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Disclosure statement
No potential conflict of interest was reported by the authors.

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