Value of Allergy Tests for the Diagnosis of Food Allergy

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Abstract
Eosinophilic esophagitis (EoE) is a chronic T helper 2-type inflammatory disorder. Concurrent allergic diseases have been observed in EoE cases at a high prevalence. The observation that EoE responds to dietary treatment suggests that EoE is an antigen-driven process. However, the pathogenesis by which allergens mediate the eosinophilic disease in the esophagus needs further clarification. In immediate-type food allergy, diagnosis is based on a careful case history followed by a search for food-specific IgE either by skin testing [skin prick test (SPT)] or in vitro (e.g. ImmunoCAP). In children with atopic dermatitis and a food allergy to milk, eggs, peanuts, fish or wheat, the SPT and in vitro determination of specific IgE show excellent sensitivity and negative predictive values, whereas the positive predictive values are low. In pollen-related secondary food allergy, sensitivity and negative predictive values of IgE testing is much lower. Consequently, oral food provocation is the gold standard for the diagnosis of food allergy. Similarly, in EoE patients, SPT, atopy patch test and in vitro determination of IgE to foods do not reliably predict food allergy, and the average positive predictive values of these allergy tests are below 50%. In conclusion, the value of allergy tests to identify triggering foods are limited, and triggering foods have to be identified by an elimination diet and consequent reintroduction of single foods under biopsy control. However, due to the high prevalence of concurrent allergic diseases among EoE patients, an allergy work-up is urgently indicated in each patient with EoE.

Introduction

Eosinophilic esophagitis (EoE) is a chronic T helper 2-type inflammatory disorder. Concurrent allergic diseases have been observed in pediatric and adult cases of EoE at a prevalence of 40–74% for allergic rhinitis, 40–70% for asthma, 4–60% for atopic dermatitis and 15–43% for IgE-mediated food allergy [1]. The observation that EoE responds to dietary treatment [1–5] and reports of intratracheal egg challenge leading in ovalbumin-sensitized mice to esophageal eosinophilia [6] suggest that EoE is at least in part a food antigen-driven process. The pathogenesis by which allergens mediate the eosinophilic disease in the esophagus, however, needs further clarification. The following article provides a summary of current food allergy diagnosis, taking into account the particular aspects of allergy testing in EoE.
Epidemiology of Food Allergy and Offending Foods

More than 30% of the general population believe to have a food allergy. The prevalence of true food allergy, however, is lower [7]. The disease affects about 8% of children below 3 years of age. The prevalence of adult food allergy is estimated to be 1–3%, which is very likely an underestimation since up to 8% of the population suffer from a birch pollen allergy and up to 80% of birch pollen allergic patients develop a food allergy to plant foods [8]. According to these figures, 5–10% of adults might suffer from a pollen-related food allergy, at least in some parts of Europe. The prevalence of IgE-mediated food allergy among patients with EoE is much higher and estimated to be 15–43% [1]. Whether there is a link between IgE-mediated food allergy in EoE patients and the activity of the esophageal disease has to be clarified in the future.

Cow’s milk, hen’s eggs, peanuts, tree nuts, fish, shellfish, soy, fruits and legumes are the foods that most frequently induce immediate-type allergic reactions. The prevalence of these specific food allergies varies with the age of the patients. Cow’s milk and hen’s eggs are worldwide the most frequent food allergies in infants and children. Milk and egg allergies are often lost with increasing age due to the development of oral tolerance. Allergies to nuts and legumes or seafood have a trend for persistence. Most food allergies with onset in the adolescence and adulthood, however, are related to inhalant allergies (so-called secondary or cross-reactive or class II food allergy). They develop as a consequence of an IgE sensitization to the aeroallergen, particularly pollen, with a subsequent cross-reaction to mainly plant foods. Therefore, plant foods are the most prevalent food allergens in the adult population [9, 10].

According to studies on EoE patients, developing resolution of the esophageal disease by targeted or empirical diets and recurrence under food reintroduction, milk, eggs, wheat and soy were the most frequent food triggers for pediatric patients with EoE [2, 5]. These triggers are in line with foods eliciting immediate-type food allergies or exacerbation of atopic dermatitis in this age group [11]. Remission of EoE after eliminating similar foods from the diets of adult patients have been observed for instance after the six-food elimination diet (elimination of milk, eggs, wheat, soy, nuts/peanuts and, fish/shellfish), which is astonishing since food allergies to eggs, milk or wheat are rarely observed among adults with an immediate-type food allergy. This observation suggests a non-IgE-mediated pathogenesis of food-triggered EoE in adults and would thus be an argument against performing IgE-based diagnosis in adult-onset EoE.

Diagnosis of Food Allergy

In immediate-type food allergy, diagnosis is based on a careful case history followed by a search for food-specific IgE either by skin testing [skin prick test (SPT)] or in vitro determination (e.g. ImmunoCAP). Positive skin or in vitro testing indicate the presence of food-specific IgE antibodies, but they do not establish the diagnosis of food allergy since sensitization to a specific food does not predict the clinical response of the sensitized patient to this respective food. Therefore, the relevance of positive IgE testing has to be proven by oral provocation testing.

SPT with Food Extracts

In children with atopic dermatitis and a primary or class I food allergy to either milk, eggs, peanuts, fish or wheat containing stable allergenic proteins, the SPT shows an excellent sensitivity of 90–100% [11]. Similarly, in that special group of patients, excellent negative predictive values of the SPT of up to 95% have been observed, but the positive predictive value has been low (<50%). For most other foods, no standardized extracts with regard to total protein content, content of single allergens or biological activity are currently available for use in the diagnosis of food allergies. Therefore, often poor correlations are observed between the clinical history or the outcome of a controlled food challenge and the skin test results.

In pollen-related secondary food allergy, the sensitivity of the SPT is much lower. For instance, with plant food extracts from celery, carrots, cherries or hazelnuts, the SPT has a sensitivity of 20–65% [12–15]. Due to the high rate of false-negative results and the low negative predictive value of the SPT using plant-derived commercial food extracts, food allergy cannot be reliably excluded in that group of patients on the basis of a negative IgE testing. Therefore, using the SPT with a food extract as a criterion for elimination of foods in EoE for adolescents and adults is not evidence based at all and not recommended since a positive SPT can be a consequence of clinically silent cross-reactivity in pollen-sensitized patients, resulting in a low specificity of this test procedure, or might be negative in patients with a true food allergy due to low sensitivity.

Atopy Patch Testing with Foods

Atopy patch testing (APT) has been investigated as a potential tool to identify foods which may cause late-type symptoms such as exacerbation of atopic dermatitis [16] or EoE [17]. This test procedure, however, is limited by standardized test substances or methods and the difficul-
ties in interpretation of results [18]. After an initial euphoria about APT facilitating the diagnosis of late-type reactions to foods in patients with atopic dermatitis, it was concluded from a recent evaluation of a large number of children with atopic dermatitis that APT does not lead to a significant reduction in the need to confirm food allergy by oral provocation testing when food-induced eczema is suspected [19, 20]. The benefit of performing ATP in addition to the SPT with foods or measurement of specific IgE to foods for the diagnosis and management of food-triggered EoE has been controversially discussed in the literature. Therefore, in the 2011 consensus recommendations for EoE it is stated that food patch testing has to be standardized and further validated in children and adults, and that evidence that APT induces a local immune response reflecting the immunopathology in patients with EoE remains to be demonstrated [1].

**In vitro Tests**

Most comments made about the SPT are also similar for the in vitro determination of specific IgE. Again a positive test result does not prove the clinical relevance of the sensitization, and a negative test might be negative due to a low extract quality. The advantage of in vitro testing, however, is the possibility to quantify food-specific IgE antibodies.

In the past, studies have been performed to generate probability curves based on the outcome of diagnostic tests, such as the diameter of wheals for the SPT or the quantity of specific IgE for in vitro tests, and the outcome of diagnostic food challenges in order to define so-called diagnostic decision points which predict clinical reactivity or tolerance [18]. The rationale behind these studies was the observation that higher levels of specific IgE or larger SPT wheals are associated with an increased likelihood of an allergic reaction. Predictive levels indicating a 95% likelihood of a clinical reactivity have been identified for milk, eggs and peanuts in children [18]: e.g. specific IgE to milk of at least 15 kU/l in US children over 2 years of age for an allergic reaction to milk and specific IgE to egg white of at least 7 kU/l for an allergic reaction to egg. However, these predictive levels lack precision since they vary significantly between different populations [18]. To date, there have been no studies indicating whether such decision points are helpful, particularly in the pediatric population, for the diagnosis or management of EoE.

**Component-Resolved in vitro Diagnosis**

Immediate-type food allergic reactions range in severity from mild local symptoms, such as the oral allergy syndrome, to associated systemic symptoms and anaphylaxis. The increasing knowledge of allergen components from various foods allow for the detection of a sensitization profile in individual patients and the comparison of such sensitization patterns with clinical presentation. This concept has been called ‘component-resolved diagnostics’. The concept of component-resolved diagnostics is based on the observation that the severity of a reaction to a particular food may depend on which allergen component the patient is sensitized to [21]. Of the major peanut seed storage proteins (Ara h 1, Ara h 2 and Ara h 3), Ara h 2 appears to be a particularly important marker of primary peanut sensitization [22]. Other allergen components that hold promise as risk markers for potentially severe allergic reactions include actinidin (Act d 1) in kiwi allergy [23] and Gly m 5 (β-conglycinin) and Gly m 6 (glycinin) in soy allergy [24]. Thus, component-resolved diagnostics offer an opportunity to assess a patient-tailored risk profile for some immediate-type food allergies and it increases the sensitivity of in vitro testing. To date, clinical responses to trigger foods in EoE have not been compared with the sensitization pattern to single allergens derived from the trigger food. Thus, we do not know whether such an approach would be helpful for the diagnosis and management of food-triggered EoE.

**Skin and in vitro Testing in EoE**

According to the study by Gonsalves et al. [3] in adult patients with EoE, the SPT with different food extracts predicted the responsible trigger food in only 13%, and 67% of the patients with an identified food trigger (re-exposure under biopsy control) were skin test negative for the respective foods. Similarly, in the recent study by Lucendo et al. [4], skin testing or in vitro testing using food extracts showed a very low sensitivity of just 22–33%. The overall specificity was 77–78% and they identified no concordance of allergy testing with food challenge results. Additionally, in a pediatric population Henderson et al. [5] observed low negative predictive values for skin testing with wheat (67%), soy (64%), eggs (56%) and milk (40%), and they concluded that their study did not provide any support of dietary plans which are based on skin test results.

Spergel et al. [2] and colleagues also identified very low negative predictive values for skin testing with milk (30%) and one of 79–90% for other foods investigated. Apart from milk (86%) the positive predictive values of skin testing with other investigated foods were low, with an average of 47%. Similar outcomes have been observed by the authors for APT. A combined use of the SPT and APT...
depicted a slightly higher negative predictive value, whereas positive predictive values remained poor with 17–82%. Elimination of SPT- and APT-positive foods resulted in a response rate of 53% in this pediatric population.

**Conclusion**

The oral food provocation testing is the gold standard for the diagnosis of immediate-type food allergy. Similarly, in EoE, which does not depict the classical reaction pattern of an immediate type food allergy, the SPT, APT and in vitro determination of IgE to foods do not reliably predict food allergy and the average positive predictive values of these allergy tests are below 50%. According to actual data, the value of allergy tests to identify triggering food allergens in EoE are limited, and triggering foods have to be identified by an elimination diet and consequent reintroduction of single foods under biopsy control. However, due to the high prevalence of allergic diseases among EoE patients, an allergy work-up is urgently indicated in each patient with EoE for the identification and management of associated allergic diseases.

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