



Guest editorial

Food allergy: diagnosis and beyond

In this issue of the *Annals*, 2 articles shed special light on the role of food challenge in the diagnosis of food allergy (FA) and on the frequency of exposures to a common food allergen, peanut, after avoidance.^{1,2} In this editorial, we use the data presented in both articles to provide a perspective on the diagnosis and natural history of FA.

Natural History of Peanut Allergy: One Patient at a Time

The question addressed by the first article¹ is one the parents often ask: “What will happen to my child with peanut allergy if exposed to peanuts?” The general notion is that exposure to peanuts is always a looming threat and that peanut allergy is always life-threatening. Few studies have addressed the natural history of peanut allergy, and most have been hampered by the lack of a confirmation of the diagnosis with an oral challenge. The diagnosis has often been made when skin test or serum specific immunoglobulin E (sIgE) level has fallen above the range of the published cutoffs predictive of clinical reactivity.

Examining the data presented in the article by Newman-Sunshine et al.,¹ from the United States, with the patients rather than the exposures as a focus, reveals that the population described is illustrative of this statement. The authors, from a tertiary referral center for FA, report on 782 patients diagnosed with peanut allergy. A total of 427 (54.6%), or more than half the patients in the study, at one time carried the diagnosis of peanut allergy without a history of ever being exposed to the food: 296 (37.9%) had no exposure to peanut neither before nor after the diagnosis and for the duration of follow-up of the study, and 131 (16.7%) patients had their exposure to peanuts only after the diagnosis of peanut allergy. The latter 131 patients break down to 100 who had an exposure “in the field” and 31 who accepted and reacted to a peanut challenge. The 100 patients who had a postdiagnosis exposure “in the field” had a total of 133 exposures, or 1.33 exposures per patient. Looking at these data from a different point of view indicates that parents of children with food allergy and the children themselves, when well instructed by their allergist, remain vigilant about exposure to peanuts, so that of the 427 patients who carried the diagnosis of peanut allergy before exposure, 296 patients, or 69.3%, managed to avoid peanuts completely. Only 7.2% accepted a food challenge.

As for the rest of the population of 355 patients who had an exposure to peanut before diagnosis, only 142 had any exposure after diagnosis, with 197 exposures, or 1.39 exposures per patient. Forty-five oral food challenges were in this group. This gives very similar results to the previous group, with 213 patients or 60% managing to avoid peanut completely and only 12.7% accepting a food challenge.

What would have been the outcome had the patients with positive tests to peanuts but without exposure, or the ones with a history of reaction and positive tests, all undergone a food challenge? The answer can be gleamed from the second article by Eller et al.² The authors report that, of 249 challenge tests with peanuts, 66% of the challenges caused reactions, with 60% having objective symptoms, removing the diagnosis of peanut allergy from 34 to 40% of the patients in whom the diagnosis would have been based only on history, skin test, or sIgE level. Although peanuts, compared with cow milk, eggs, and hazelnut, gave the highest percentage of severe reactions to the challenge; this occurred mostly in subjects 15 years of age and older. This strongly suggests that clinicians should seize the opportunity, when the diagnosis of peanut allergy is most likely to be made and when food challenges are least likely to produce severe reactions, in children younger than 4 years, to confirm the diagnosis by challenge testing, before a lifetime of strict avoidance is prescribed. This is the position of the National Institute of Allergy and Infectious Disease Expert Panel on Food Allergy.³ Conversely, the standardization of food challenge procedure has not been without its own challenges.

The Challenges of Oral Food Challenge

Eller et al.² attempted to determine the thresholds of food doses that can elicit reactions in individual patients, hypothesizing that the thresholds for various foods are comparable if adjusted for the protein content. The study reviews 781 challenges to cow's milk, hen's egg, peanut, and hazelnut in 487 subjects ages 0.5 to 73.5 years at 1 center in Denmark, performed by a standardized titrated challenge procedure. Open challenges were used for children younger than 4 years, and double-blind, placebo-controlled challenges were used in older subjects. The authors looked at 2 parameters: the highest dose that caused no symptoms and the lowest dose that elicited allergic symptoms, because the “true” threshold dose should be between those 2 doses.

The study has several merits. The challenges were done by the same procedure and were double-blind, placebo-controlled in older children and adults. Skin testing was done by the same method using prick-by-prick technique, and the sIgE was measured by the same assay (ImmunoCAP; Phadia AB, Uppsala, Sweden). However, the first challenge dose was different between open and blind procedures, and it varied from 1 food to another. Also, the material used for skin testing or sIgE testing was probably not of the same immunogenicity as the usually consumed food. Reactions occurred in 57% of the challenges, 7% of which were to the first dose, and were the highest, 19%, with cow's milk, indicating that the starting dose for cow's milk should be less than 5 ml. Another interesting finding is the higher risk of severe reactions in subjects 15 years of age and older compared with children younger than 4 years.

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Contrary to logical expectations, there was weak or no correlation between the threshold dose causing objective symptoms and the degree of positivity to skin test or sIgE. This underscores the suboptimal reliability of these 2 tests that reflect sensitization rather than clinical allergy. In interpreting the test result in any individual subject, several factors need to be considered: total IgE level, patient's age, type and severity of allergy manifestation, food allergen, degree of exposure to the food at the time of testing, and duration of avoidance of the food before the test.⁴ Although in this study peanut caused more severe reactions than cow's milk, egg, or hazelnut, this should not mean that peanut is the most allergenic food in general. In a study by Clark et al,⁵ cashew was responsible for more severe reactions than peanut.

Another interesting finding is that the threshold dose of peanut was much higher than that reported in previous studies. Multiple factors can be responsible for such a discrepancy; most important are the individual's degree of sensitivity to certain epitopes, the type of manifestations, and genetic variations.

The corollary is that the safe first dose of food challenge cannot be "standardized" but rather individualized; neither "too high" to be risky nor "too low" to waste time in performing the procedure. Herein is the expertise of the performer.⁶ The cumulative challenge dose should be at least equivalent to the usually consumed quantity of the food. Preliminary results of the use of the component resolved testing suggests a better, but not perfect, prediction of the degree of anticipated reaction in individual patients for specific foods.^{7,8}

In summary, the 2 articles provide a useful insight into the diagnosis and natural history of FA, and their results should encour-

age the practicing allergist and the FA patients/parents to appropriately use the oral challenge test to confirm the diagnosis.

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