

Food allergy: Are we getting closer to a cure?

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This month's Journal theme highlights recent advances in food allergy. A National Institutes of Health/National Institute of Allergy and Infectious Diseases-sponsored Expert Panel report, published in the Journal at the end of 2010, provided guidelines for the diagnosis and management of food allergy.^{1,2} The current theme issue builds on the recognition of food allergy as a significant public health problem by examining issues related to the epidemiology, risk factors, mechanisms, and new treatments on the horizon for this common problem seen by both allergists and primary care providers.

EPIDEMIOLOGY AND DIAGNOSIS

In the current issue of the Journal, Sicherer³ reviews the challenge of determining an exact prevalence for food allergy. Studies have reported a wide range for prevalence of food allergy.⁴⁻⁹ The inability to pinpoint the prevalence of food allergy stems from multiple factors including misclassification of adverse reactions to foods, lack of uniform diagnostic criteria, potential racial differences, varied clinical phenotypes, and differences intrinsic to each age group or reactivity by food type. Despite uncertainty about the exact prevalence of food allergy, there is little doubt that food allergy is a common problem.

Establishing whether the prevalence of food allergy is increasing has been an even more daunting task. This challenge is thwarted by methodologic concerns including differences in criteria used for diagnosis of food allergy and changes in target populations. Nevertheless, when similar methodologies were applied over time to large populations, there was evidence that the rates of food allergy for particular foods, such as peanuts and tree nuts, have been increasing in prevalence. In a recent US study¹⁰ that administered surveys in a similar fashion in 1997, 2002, and 2008, the rates of surrogate-reported allergy in children increased significantly for tree nuts (0.6% to 1.2% to 2.1%) and peanut (0.4% to 0.8% to 1.4%). Methodologic concerns in this study have been raised, including decreasing participation rates and increased perception of food allergy. However, evidence for increases in food allergy rates is also supported by a recent report of greater numbers of emergency department visits for food-induced anaphylaxis over time.¹¹ In addition, there are concerns

that food allergies are more persistent than previously appreciated.¹²

The recent publication of uniform guidelines for the diagnosis of food allergy is a major advance in management of this condition.^{1,13} Developing accurate criteria for diagnosis of food allergy, short of doing a time-consuming double-blind, placebo-controlled food challenge, is an important goal for research to progress more rapidly in this area.¹⁴ Considerable work is ongoing to develop clinically relevant immunologic tests that can predict severity of reactions to different foods and the natural history of various food allergies once a diagnosis is made.¹⁵⁻²⁰

RISK FACTORS AND GENETICS

Recent studies have identified potential genetic and environmental risk factors that could significantly influence the development of food allergy. Vassallo and Camargo²¹ proposed that vitamin D deficiency may underlie the changing pattern of food allergy through alteration in the intestinal barrier and promotion of sensitizing immune responses. Two population-based studies^{22,23} have recently concluded that delaying the introduction of milk and egg into the diet increased the odds ratio of developing allergy to these foods. These studies support the concept that oral exposure promotes immune tolerance, and excessive delays in the introduction of foods into the diet may allow sensitization to proceed through intermittent oral and environmental exposures first proposed by Lack and his colleagues²⁴ in their observations on peanut allergy. However, the timing of exposure will likely be tricky, as suggested by a study from the National Institutes of Health/National Institute of Allergy and Infectious Diseases-funded Consortium of Food Allergy Research.²⁵ In their report, it was found that maternal ingestion of peanut during pregnancy had a positive dose-response association with the risk of infants having elevated peanut-specific IgE antibodies. These articles suggest that a complex combination of various dietary, environmental, and genetic factors influences food allergy outcomes, and more systematic controlled studies are needed before optimal prevention strategies can be developed.

Food allergy often occurs in association with atopic dermatitis (AD). Recent studies have demonstrated that filaggrin gene mutations play a critical role in reduced skin barrier function, enhanced cutaneous allergen absorption, and systemic allergen sensitization.^{26,27} Importantly, a study by Fox et al²⁸ found that high levels of environmental exposure to peanut during infancy were a significant risk factor for the development of peanut allergy independent of maternal peanut ingestion during pregnancy or lactation.

Consistent with the notion that cutaneous exposure to peanuts may be an important route of allergen sensitization, Brown et al²⁹ report in the current issue of the Journal that there is a significant association between the occurrence of filaggrin gene mutations and peanut allergen sensitization. Although this finding is potentially exciting, caution needs to be exercised before jumping on

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the band wagon of extending environmental control from aeroallergens to including elimination of household ingestion of food allergens! The potential problem with interpreting data implicating peanut allergy in patients with AD is that filaggrin mutations are a significant risk for AD and systemic atopic sensitization. In addition, peanut allergy often occurs in patients with AD. In the current report, the data become weaker when the investigators deal with these complex interrelationships because they rely on 71 cases of peanut allergy and controls collected from various studies. Clearly, additional, better controlled studies are needed with larger sample sizes matching AD severity and IgE sensitization in the peanut-allergic group versus the non-peanut-allergic group. Nevertheless, this article is an important first step in opening up a new area of research in food allergy.

Aside from genetic defects in filaggrin expression, recent studies have demonstrated that there are multiple defects in terminal differentiation of the cornified envelope of patients with AD, which leads to barrier dysfunction and may thereby enhance allergen absorption through the skin and increase IgE responses to food allergens in the patient's environment.³⁰ It will also be important to determine whether environmental exposure and defects in skin barrier predispose to sensitization with other foods that patients with AD often become allergic to, including eggs and milk.

IMMUNE MECHANISMS OF FOOD ALLERGY

In the current issue of the Journal, Vickery et al³¹ review the complex mechanisms that may underlie food allergy. Factors that prevent digestion of food allergens such as intrinsic properties of the food structure or coadministration of antacids have been reported to interfere with oral tolerance induction. Immune factors required for immune tolerance to foods include induction of regulatory T cells or secretory IgA that bind luminal antigens. In the Consortium of Food Allergy Research cohort,³² allergen-induced *IL4* expression was associated with clinical allergy to milk and IgE sensitization to milk and peanut. In an animal model, peanut allergy was mediated through a mast cell–IL-13 pathway, supporting the importance of T_H2 responses in the development of food allergy.³³

Gastrointestinal epithelial dysfunction is also thought to contribute to food allergy by increasing sensitization through a leaky barrier and enhanced expression of thymic stromal lymphopoietin, which result in T_H2 responses. The structural integrity of the gut barrier depends on epithelial junction complexes and tight junctions. In the current issue of the Journal, the observation by De Benedetto et al³⁴ of reduced expression of the tight junction, claudin, in the skin of patients with AD is of particular interest given the association of AD with food allergy. Furthermore, it adds another level of complexity to the heterogeneity of mechanisms underlying barrier dysfunction in AD. If gene variants lead to reduced expression of claudin and barrier dysfunction in AD skin, it will be of interest to determine whether such individuals also have reduced claudin expression in their gastrointestinal tracts as well as an association of claudin gene variants with the development of food allergy.

NEW TREATMENTS

In the current issue, Nowak-Węgrzyn and Sampson³⁵ summarize new treatment approaches targeting food allergies. Given the potential of serious reactions caused by accidental food allergen

ingestion,^{36,37} identification of a cure for food allergy is the highest priority in food allergy research. Approaches being pursued include both food allergen-specific and nonspecific treatments. The food allergen-specific approaches include oral, sublingual, and epicutaneous immunotherapy (desensitization) with native food allergens, and mutated recombinant proteins, which have reduced IgE-binding activity, and are being studied for their ability to suppress food-allergic responses.³⁸⁻⁴¹ Food-specific approaches are most advantageous in targeting specific foods that cause severe IgE-mediated anaphylactic reactions such as peanut, tree nuts, and shellfish or are very common in children such as cow's milk and hen's egg. On the basis of the successes of immunotherapy in seasonal allergic rhinitis, this approach may come closest to a "cure" for the respective food allergen being targeted, although much work remains before this can be introduced into clinical practice.⁴²

Nonspecific approaches include humanized monoclonal anti-IgE antibodies, which can increase the threshold dose for food allergen in the majority of adults with food allergy.⁴³ A Chinese herbal formulation⁴⁴ that prevents peanut-induced anaphylaxis in a mouse model, potentially by providing protection through a reduction in mast cell and basophil numbers as well as the suppression of IgE-mediated mast cell activation, has also entered clinical trials. For patients with severe food-induced anaphylaxis, monoclonal anti-IgE antibodies could potentially also be used to reduce the severity of adverse events during food immunotherapy by using an approach similar to that reported for aeroallergen immunotherapy.⁴⁵

CONCLUSION AND FUTURE DIRECTIONS

There are few diseases that spark more debate regarding causation or diagnostic criteria than food allergy. The commitment by federal agencies and various foundations to fund more research in food allergy is a big step forward toward developing an effective treatment for this common, potentially life-threatening condition that can significantly affect the lives of patients and their families. Favorable results involving oral and sublingual immunotherapy to specific food allergens as well as clinical trials with anti-IgE and a Chinese herbal formulation provide optimism that we are closer to a "cure" for food allergy. However, different patterns of response to the various treatments, including subsets of patients who lack benefits, suggest the need for more careful identification of patients likely to benefit from each form of therapy. Before these treatments can be used in clinical practice, additional studies are needed to determine optimal maintenance doses, ideal duration, degree of protection, efficacy for different ages, severity and type of food allergies responsive to treatment. In addition, questions remain about long-term safety and mechanisms by which the different treatments work. However, the current theme issue strongly suggests that the field of food allergy is poised for clinically important advances.

REFERENCES

1. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: summary of the NIAID-sponsored Expert Panel report. *J Allergy Clin Immunol* 2010;126:1105-18.
2. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored Expert Panel. *J Allergy Clin Immunol* 2010;126:S1-S58.
3. Sicherer SH. Epidemiology of food allergy. *J Allergy Clin Immunol* 2011;127:594-602.

4. Clark S, Espinola J, Rudders SA, Banerji A, Camargo CA Jr. Frequency of US emergency department visits for food-related acute allergic reactions. *J Allergy Clin Immunol* 2011;127:682-3.
5. Kotz D, Simpson CR, Sheikh A. Incidence, prevalence, and trends of general practitioner recorded diagnosis of peanut allergy in England, 2001-2005. *J Allergy Clin Immunol* 2011;127:623-30.
6. Ben-Shoshan M, Harrington DW, Soller L, Fragapane J, Joseph L, St Pierre Y, et al. A population-based study on peanut, tree nut, fish, shellfish, and sesame allergy prevalence in Canada. *J Allergy Clin Immunol* 2010;125:1327-35.
7. Shek LP, Cabrera-Morales EA, Soh SE, Gerez I, Ng PZ, Yi FC, et al. A population-based questionnaire survey on the prevalence of peanut, tree nut, and shellfish allergy in 2 Asian populations. *J Allergy Clin Immunol* 2010;126:324-31.
8. Liu AH, Jaramillo R, Sicherer SH, Wood RA, Bock SA, Burks AW, et al. National prevalence and risk factors for food allergy and relationship to asthma: results from the National Health and Nutrition Examination Survey 2005-2006. *J Allergy Clin Immunol* 2010;126:798-806.
9. Vereda AM, van Hage M, Ahlstedt S, Ibañez MD, Cuesta-Herranz J, van Odijk J, et al. Peanut allergy: clinical and immunologic differences among patients from 3 different geographic regions. *J Allergy Clin Immunol* 2011;127:603-7.
10. Sicherer SH, Munoz-Furlong A, Godbold JH, Sampson HA. US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. *J Allergy Clin Immunol* 2010;125:1322-6.
11. Rudders SA, Banerji A, Vassallo MF, Clark S, Camargo CA Jr. Trends in pediatric emergency department visits for food-induced anaphylaxis. *J Allergy Clin Immunol* 2010;126:385-8.
12. Savage JH, Kaeding AJ, Matsui EC, Wood RA. The natural history of soy allergy. *J Allergy Clin Immunol* 2010;125:683-6.
13. Fiocchi A. DRACMA (Diagnosis and Rationale for Action Against Cow's Milk Allergy): a summary report. *J Allergy Clin Immunol* 2010;126:119-28.
14. DunnGalvin A, Deirdre D, Cullinane C, Stenke E, Keeton D, Erlewyn-Lajunesse M, Roberts GC, et al. Highly accurate prediction of food challenge outcome using routinely available clinical data. *J Allergy Clin Immunol* 2011;127:633-9.
15. van Nieuwaal NH, Lasfar W, Meijer Y, Kentie PA, Flinterman AE, Pasmans SG, et al. Utility of peanut-specific IgE levels in predicting the outcome of double-blind, placebo-controlled food challenges. *J Allergy Clin Immunol* 2010;125:1391-2.
16. Geroldinger-Simic M, Zelniker T, Aberer W, Ebner C, Egger C, Greiderer A, et al. Birch pollen-related food allergy: clinical aspects and the role of allergen specific IgE and IgG4 antibodies. *J Allergy Clin Immunol* 2011;127:616-22.
17. Le T-M, Fritsche P, Bublin M, Oberhuber C, Bulley S, van Hoffer E, et al. Differences in the allergenicity of 6 different kiwifruit cultivars analyzed by prick-to-prick testing, open food challenges, and ELISA. *J Allergy Clin Immunol* 2011;127:677-9.
18. Nicolaou N, Murray C, Belgrave D, Poorafshar M, Simpson A, Custovic A. Quantification of specific IgE to whole peanut extract and peanut components in prediction of peanut allergy. *J Allergy Clin Immunol* 2011;127:684-5.
19. Nicolaou N, Poorafshar M, Murray C, Simpson A, Winell H, Kerry G, et al. Allergy or tolerance in children sensitized to peanut: prevalence and differentiation using component-resolved diagnostics. *J Allergy Clin Immunol* 2010;125:191-7.
20. Savilahti EM, Rantanen V, Lin JS, Karinen S, Saarinen KM, Goldis M, et al. Early recovery from cow's milk allergy is associated with decreasing IgE and increasing IgG4 binding to cow's milk epitopes. *J Allergy Clin Immunol* 2010;125:1315-21.
21. Vassallo MF, Camargo CA Jr. Potential mechanisms for the hypothesized link between sunshine, vitamin D, and food allergy in children. *J Allergy Clin Immunol* 2010;126:217-22.
22. Katz Y, Rajuan N, Goldberg MR, Eisenberg E, Heyman E, Cohen A, et al. Early exposure to cow's milk protein is protective against IgE-mediated cow's milk protein allergy. *J Allergy Clin Immunol* 2010;126:77-82.
23. Koplin JJ, Osborne NJ, Wake M, Martin PE, Gurrin LC, Robinson MN, et al. Can early introduction of egg prevent egg allergy in infants? A population-based study. *J Allergy Clin Immunol* 2010;126:807-13.
24. Du Toit G, Katz Y, Sasieni P, Mesher D, Maleki SJ, Fisher HR, et al. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. *J Allergy Clin Immunol* 2008;122:984-91.
25. Sicherer SH, Wood RA, Stablein D, Lindblad R, Burks AW, Liu AH, et al. Consumption of peanut during pregnancy is associated with peanut sensitization in atopic infants. *J Allergy Clin Immunol* 2011;127:594-602.
26. Leung DY. Our evolving understanding of the functional role of filaggrin in atopic dermatitis. *J Allergy Clin Immunol* 2009;124:494-5.
27. Barnes KC. An update on the genetics of atopic dermatitis: scratching the surface in 2009. *J Allergy Clin Immunol* 2010;125:16-29.
28. Fox AT, Sasieni P, du Toit G, Syed H, Lack G. Household peanut consumption as a risk factor for the development of peanut allergy. *J Allergy Clin Immunol* 2009;123:417-23.
29. Brown SJ, Asai Y, Cordell HJ, et al. Loss-of-function variants in the filaggrin gene are a significant risk factor for peanut allergy. *J Allergy Clin Immunol* 2011;127:661-7.
30. Guttman-Yassky E, Suarez-Farinas M, Chiricozzi A, Nograles KE, Shemer A, Fuentes-Duculan J, et al. Broad defects in epidermal cornification in atopic dermatitis identified through genomic analysis. *J Allergy Clin Immunol* 2009;124:1235-44.
31. Vickery BP, Scurlock AM, Jones SM, Burks AW. Mechanisms of immune tolerance relevant to food allergy. *J Allergy Clin Immunol* 2011;127:576-84.
32. Sicherer SH, Wood RA, Stablein D, Burks AW, Liu AH, Jones SM, et al. Immunologic features of infants with milk or egg allergy enrolled in an observational study (Consortium of Food Allergy Research) of food allergy. *J Allergy Clin Immunol* 2010;125:1077-83.
33. Wang M, Takeda K, Shiraishi Y, Okamoto M, Dakhama A, Joetham A, et al. Peanut-induced intestinal allergy is mediated through a mast cell-IgE-FcεpsilonRI-IL-13 pathway. *J Allergy Clin Immunol* 2010;126:306-16.
34. De Benedetto A, Rafaels NM, McGirt LY, Ivanov AI, Georas SN, Cheadle C, et al. Tight junction defects in atopic dermatitis. *J Allergy Clin Immunol* 2011;127:773-86.
35. Nowak-Węgrzyn A, Sampson HA. Future therapies for food allergies. *J Allergy Clin Immunol* 2011;127:558-73.
36. Sicherer SH, Sampson HA. Food allergy. *J Allergy Clin Immunol* 2010;125:S116-25.
37. Ford LS, Taylor SL, Pacenza R, Niemann LM, Lambrecht DM, Sicherer SH. Food allergen advisory labeling and product contamination with egg, milk, and peanut. *J Allergy Clin Immunol* 2010;126:384-5.
38. Prickett SR, Voskamp AL, Dacumos-Hill A, Symons K, Rolland JM, O'Hehir RE. Ara h 2 peptides containing dominant CD41 T-cell epitopes: candidates for a peanut allergy therapeutic. *J Allergy Clin Immunol* 2011;127:608-15.
39. Kim EH, Bird JA, Kulis M, Laubach S, Pons L, Shreffler W, et al. Sublingual immunotherapy for peanut allergy: clinical and immunologic evidence of desensitization. *J Allergy Clin Immunol* 2011;127:640-6.
40. Blumchen K, Ulbricht H, Staden U, Dobberstein K, Beschoner J, de Oliveira LC, et al. Oral peanut immunotherapy in children with peanut anaphylaxis. *J Allergy Clin Immunol* 2010;126:83-91.
41. Dupont C, Kalach N, Soulaines P, Legoue-Morillon S, Piloquet H, Benhamou PH. Cow's milk epicutaneous immunotherapy in children: a pilot trial of safety, acceptability, and impact on allergic reactivity. *J Allergy Clin Immunol* 2010;125:1165-7.
42. Thyagarajan A, Varshney P, Jones SM, Sicherer S, Wood R, Vickery BP, et al. Peanut oral immunotherapy is not ready for clinical use. *J Allergy Clin Immunol* 2010;126:31-2.
43. Sampson HA, Leung DYM, Burks W, Lack G, Bahna SL, Jones SM, et al. A phase II, randomized, double-blind, parallel-group, placebo-controlled, oral food challenge trial of XOLAIR (omalizumab) in peanut allergy. *J Allergy Clin Immunol* 2011 (in press); doi: 10.1016/j.jaci.2011.01.051.
44. Song Y, Qu C, Srivastava K, Yang N, Busse PJ, Zhaom W, et al. Food Allergy Herbal Formula-2 protection against peanut anaphylactic reaction is via inhibition of mast cells and basophils. *J Allergy Clin Immunol* 2010;127:1208-17.
45. Massanari M, Nelson H, Casale T, Busse W, Kianifard F, Geba GP, et al. Effect of pretreatment with omalizumab on the tolerability of specific immunotherapy in allergic asthma. *J Allergy Clin Immunol* 2010;125:383-9.