EDITORIAL REVIEW

Peanut, tree nut and seed allergies

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Introduction

In the past year, there have been significant advances in our overall knowledge base concerning peanut, tree nut and seed food allergies. These plant foods share the unfortunate distinction of association with a persistent food-allergic state in the majority of individuals affected. Further information on peanut and tree nut allergens, cross-reactivity and data on sesame, sunflower or other seed allergies are still sorely needed. In spite of increasing knowledge and public awareness of food allergies – including the shift away from early (on purpose) introduction of peanut in the diet and the favorable trend towards increased breastfeeding – serious food allergy continues to develop, indicating the potential for research and discovery in the area of primary sensitization and tolerance towards environmental and food proteins. Herein, we will review a few of the recent reports on peanut, tree nut and seed allergies.

Epidemiology

Studies continue to suggest an increase in the prevalence of clinical peanut allergy among children – this is alarming because the follow-up periods between similar surveys have been as short as 5 years [1,2••]. Sicherer and colleagues [3] conducted a second random digit dial telephone survey 5 years after the original study and determined the self-reported prevalence of peanut or tree nut allergy in combined adults and children to be 1.4%. In the most recent 2002 survey, the overall prevalence in the general population was similar for peanut and tree nut allergy at 1.04% but, significantly, the rate of reported clinical reactivity to peanuts among children was doubled in this second survey, from 0.4% to 0.8% ($P = 0.05$). Among the tree nut allergies reported, walnut was again the most common, followed by cashew and almond [2••].

In Montreal, Kagan *et al.* [4••] administered questionnaires to families of 7768 children, ranging from kindergarten to third grade, at randomly selected elementary school sites, with 4339 families choosing to participate. The study went further than the random digit dial telephone surveys in that the histories were corroborated with skin prick testing, and in those with uncertain histories with a positive skin prick test, quantification of specific IgE followed by oral peanut food challenges (if the specific IgE level was less than 15 kU/l) were performed. Using these diagnostic criteria, a surprisingly high prevalence of peanut allergy was suggested in this population (1.34%).

A factor that is postulated to have contributed to peanut allergy in the UK is the cutaneous exposure to ultra-low doses of peanut antigens in peanut oil found in diaper rash creams and emollients which have been applied to the skin of infants with eczema or diaper rash. Lack *et al.* [5] took advantage of the unique opportunity afforded by a geographic cohort study, the Avon Longitudinal Study of Parents and Children, to prospectively gather detailed information related to the development of peanut allergy. The data on skin emollients were obtained in a retrospective telephone interview. Peanut allergy was reported in 49 of 13 973 children (0.4%) born in 1991–92 and 36 were available to undergo skin testing at age 4–6 years old. Twenty-nine had positive skin tests and 23 had positive double-blind, placebo-controlled food challenges to peanut. Multivariate logistic regression revealed the aforementioned association with topical peanut oil in emollients and also with a family history of peanut allergy, the presence of oozing, crusted rash and, to a lesser extent, the consumption of soy formulas. We do not know if peanut oil has been included in diaper rash creams and emollients in Canada, but it is not contained in the main brands used in the USA; other associations should obviously be explored, but the findings are intriguing.

Allergens

Thermal modification can enhance or reduce the allergenicity of proteins. In this issue, Maleki [6] reviewed the effects of roasting on the enhancement of trypsin inhibitor function of the peanut allergen Ara h 2, a finding that will open up new areas of investigation into modifying food allergencity. Interestingly, Ara h 2 subjected to roasting was shown to protect Ara h 1 from proteolytic digestion when co-incubated [7••]. Whether other 2S albumin allergens exhibit trypsin inhibitor function remains to be seen, but resistance to digestion

in simulated gastric fluid has been recently shown for the 2S albumins Ber e 1 from Brazil nut and SFA-8 from sunflower [8].

Dibbern *et al.* [9•] published a new methodology for studying IgE–peanut antigen functional interactions. They used rat basophil leukemia cells expressing human Fc epsilon RI and exposed the cells to sera IgE from human peanut allergic patients to sensitize the cells. They showed that subsequent incubation with crude peanut extract could specifically induce degranulation. This system may prove useful in studying individual allergens and their unique potential to elicit degranulation as a functional assay using human sera – a resource more readily available than whole blood for histamine release assays or CD63 expression. Such an assay may be useful to tease out which antigens are more likely to be clinically relevant out of multiple antigens that bind IgE (e.g. Ara h 2 versus Ara h 3).

Tree nut allergens have recently been extensively reviewed [10••]. In the past year, a few new allergens have been characterized by cloning: hazelnut Cor a 8 (lipid transfer protein), and cashew Ana o 2 (legumin group) [11,12]. Case reports and small series on cross-reactivity in multiple tree nut allergy (nonpollen related) support the hypothesis that IgE to homologous seed proteins besides lipid transfer protein can result in clinical allergy upon ingestion of different tree nuts. Such relationships were seen in a case of walnut-induced anaphylaxis in which IgE cross-reactivity was clearly demonstrated by inhibition immunoblotting with brazil nut and hazelnut [13]. The issue of clinically relevant cross-reactive IgE versus irrelevant cross-reactivity will need further study, including between peanut and tree nuts. de Leon and colleagues [14] showed low cross-reactivity between almond, brazil nut, hazelnut and peanut and no cross-reactivity *in vitro* between cashew and peanut using sera from four patients. Furthermore, Rance *et al.* [15] did not find the co-existence of peanut allergy and cashew allergy in their recent description of 42 children with cashew allergy, although some were also clinically allergic to pistachio. Very little has been reported in the literature so far on the less common tree nuts. There was a case report from Spain describing two children who experienced anaphylaxis to pine nut who both demonstrated IgE to polypeptides at about 17 kDa – similar to another case report. However, the antigen has not been identified [16,17].

Also from Spain, a lentil allergen in the vicilin family has been characterized recently and the gene encoding the precursor has been cloned [18]. Lentil allergy is important in the Mediterranean region. Sesame seed is considered an emerging important food allergen source worldwide, but especially in Israel. Dalal and colleagues [19•] described 30 children sensitized to sesame. The mean age of the first allergic reaction was 11.7 months, with anaphylaxis in seven infants on presentation. The severity of this food allergy is further appreciated by the report of Morisset and colleagues in France [20••], who reported that five of 12 sesame seed oral challenges resulted in an asthmatic response and two individuals challenged with sesame oil developed anaphylactic shock. Similarly, as in peanuts and tree nuts, seed storage proteins represent the major allergens in sesame seeds [21].

Therapy

Much media focus this past year has been on the published clinical trial using a monoclonal anti-IgE, TNX-901, in peanut allergy [22••]. The group of patients receiving the highest dose of 450 mg of TNX-901 subcutaneously on a weekly basis for 4 weeks had a significant increase in the threshold dose of peanut flour eliciting symptoms. Almost a quarter were able to tolerate ingestion of 8 g of peanut flour in capsules, a remarkable response; however, approximately 25% of the patients receiving the highest dose reacted to a challenge dose of 500 mg or less of peanut flour, corresponding to 1–2 peanut kernels. The characteristics of the peanut immune response of these particular patients were not published in a secondary analysis, which would have yielded interesting information even if the numbers were small; that is, it would have been useful to see if there were differences between those who responded significantly and those who could still be considered 'at risk' (for accidental reaction) in the specific titer of IgE to peanut, age, the specific peanut antigens recognized, and the linear epitopes recognized on those antigens [23••]. Although TNX-901 is no longer in clinical development, a clinical trial is due to begin in 2004 utilizing another monoclonal anti-IgE, omalizumab, for peanut allergy.

Conclusion

Peanut, tree nut and seed allergy are critically important food allergies and the number of laboratories and clinical units addressing these topics has increased significantly. Full characterization of the allergens is within reach, as is the extension of mechanistic studies and therapeutic trials.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

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2 •• Sicherer SH, Munoz-Furlong A, Sampson HA. Prevalence of peanut and tree nut allergy in the United States determined by means of a random digit dial telephone survey: a 5-year follow-up study. J Allergy Clin Immunol 2003; 112:1203–1207.
This study demonstrated the doubling of the prevalence rate of peanut allergy among children compared with the previous survey just 5 years before.

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4 •• Kagan RS, Joseph L, Dufresne C, *et al*. Prevalence of peanut allergy in primary-school children in Montreal, Canada. J Allergy Clin Immunol 2003; 112:1223–1228.
This study used skin prick testing, in-vitro assays and food challenges when needed to confirm peanut allergy.

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6 Maleki S. Food processing: effects on allergenicity. Curr Opin Allergy Clin Immunol (in press)

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This work provides further insight into the increased allergenicity of peanut after roasting.

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This comprehensive review provides an update on the most recent findings in tree nut allergens.

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12 Wang F, Robotham JM, Teuber SS, *et al*. Ana o 2, a major cashew (Anacardium occidentale L) nut allergen of the legumin family. Int Arch Allergy Immunol 2003; 132:27–29.

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14 de Leon MP, Glaspole IN, Drew AC, *et al*. Immunological analysis of allergenic cross-reactivity between peanut and tree nuts. Clin Exp Allergy 2003; 33:1273–1280.

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19 • Dalal I, Binson I, Levine A, *et al*. The pattern of sesame sensitivity among infants and children. Pediatr Allergy Immunol 2003; 14:312–316.
This clinical series highlights the severity of the systemic allergic reactions to sesame.

20 •• Morisset M, Moneret-Vautrin DA, Kanny G, *et al*. Thresholds of clinical reactivity to milk, egg, peanut and sesame in immunoglobulin E-dependent allergies: evaluation by double-blind or single-blind placebo-controlled oral challenges. Clin Exp Allergy 2003; 33:1046–1051.
The French team of allergologists describes the findings of their very large series of threshold evaluations.

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22 •• Leung DYM, Sampson HA, Yunginger JW, *et al*. Effect of anti-IgE therapy in patients with peanut allergy. New Engl J Med 2003; 348:986–993.
A potential therapy for severe food allergy is presented that would protect patients in the case of accidental small ingestions via cross-contamination or mislabeling.

23 •• Beyer K, Ellman-Grunther L, Jaravinen KM, *et al*. Measurement of peptide-specific IgE as an additional tool in identifying patients with clinical reactivity to peanuts. J Allergy Clin Immunol 2003; 112:202–207.
Based on this study, the identification of linear IgE epitopes may warrant expansion to multiple other foods to help define the risk of persistence of the allergy or of the severity of a reaction.