

Peanut allergy

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Purpose of review

To highlight recent advances in management of peanut allergy.

Recent findings

Peanut allergy presents during early childhood. The prevalence of peanut allergy in children in developed countries appears to be increasing. Several factors, such as peanut-specific or environmental, are hypothesized as contributing to increased prevalence. However, there is no consensus on this matter. Component-related diagnostic tests are being explored to characterize clinical sensitivity. Currently, the primary treatment includes avoidance of peanut and immediate treatment of anaphylaxis. Recent peanut oral immunotherapy (OIT) trials achieved successful desensitization to peanuts in study participants, which may benefit many patients. Newer prospective studies are exploring effects of early high-dose peanut protein introduction versus avoidance in high-risk infants and development of peanut tolerance [Learning Early About Peanut Allergy (LEAP) study]. Several other immunotherapeutic approaches are being investigated in animal models.

Summary

There is no cure for peanut allergy. Peanut oral immunotherapy offers a potential treatment for desensitization.

Keywords

desensitization, novel diagnostics, peanut allergy prevalence

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Introduction

Peanut allergy is a major health concern worldwide, particularly in developed countries. Peanut allergy affects more than 1% of the US population [1]. Reactions to peanuts and tree nuts are often severe and also persist lifelong. Peanut and tree nut allergy accounts for approximately 80% of fatal and near-fatal anaphylactic reactions to food [2]. Peanut allergy causes a significant psychological burden on both the allergic individuals and their families [3]. Although there is increased awareness of peanut allergy, there is no satisfactory therapy available to prevent or reverse the disease.

In the past few years, studies to understand factors related to increasing prevalence, effects of food processing and oral peanut immunotherapy have been published in recent literature.

Prevalence of peanut allergy

Prevalence studies of peanut allergy in children suggested a dramatic increase. Estimates from the United Kingdom suggested a two-fold increase, from 0.5 to 1.0% among young children between 1989 and 1994–1996 [4]. Similar estimates from studies [5] in the USA suggested

an increase from 0.4 to 0.8% between 1997 and 2002. A recent study [6^{*}] evaluating time trend in peanut allergy in three cohorts of children born in the same geographical area, Isle of Wight, UK, however, demonstrated no significant change in peanut allergy since the late 1990s (1994–2002). Another retrospective cohort study of 778 participants (age 4 months to 66 years) diagnosed with peanut allergy in Capitol Territory, Australia, showed mild increasing prevalence trend but unchanged characteristics of peanut allergy in the last 13 years. However, a later onset of first reaction (>72 months) was associated with greater risk of anaphylaxis, which is contrary to previous knowledge [7^{*}]. Retrospective studies like these are limited for interpretations. Although scientists continue to explore causative factors for development of peanut allergy, none is agreed upon. Various factors including peanut-specific factors like amount of consumption, food processing or other influences like maternal/infant diet, hygiene hypothesis, sunlight exposure and vitamin D, use of antacids or nonoral exposure to peanut proteins are thought to be contributory. Studies eliminating food allergens including peanut during pregnancy, lactation and early infancy have consistently failed to prevent development of immunoglobulin (Ig) E-mediated food allergy. The issue about timing of peanut introduction in diet continues to be discussed. Du Toit *et al.* [8] demonstrated

a 10-fold higher prevalence in Jewish children in the UK than that in Jewish children in Israel, in spite of early (8–14 months) and generous amount of peanut in diet. The authors concluded that the difference was not accounted for by difference in atopy, social class, genetic background or peanut allergenicity. The authors suggested that the lowered prevalence was due to earlier introduction and consuming higher quantities of peanut in the first year of life. This study suggested alternate routes of peanut sensitization and also that early oral exposure to peanut promotes tolerance. Fox *et al.* [9**] published an interesting study to indicate household peanut consumption as a risk factor for development of peanut allergy. The authors showed that weekly household peanut consumption in 133 peanut-allergic cases was significantly elevated (18.8 g) compared with 150 controls without allergy (6.9 g) and 160 high-risk (egg allergy) controls (1.9 g). The maternal peanut consumption during pregnancy and lactation had no effect. The authors concluded that high levels of environmental exposure to peanut during infancy appear to promote sensitization. Hopefully, interventional studies like Learning Early About Peanut Allergy (LEAP study), a multinational controlled trial exploring whether early introduction of high doses of peanut protein to high-risk infants is more effective than avoidance therapy, will answer these important questions [10] (<http://www.leapstudy.co.uk/index.html>). There is a significant knowledge gap in our current understanding of development of peanut allergy. Boulay *et al.* [11] have reviewed evidence for relevance of various factors hypothesized to have association with prevalence of peanut allergy and also highlight the questions that need to be addressed in future research.

Peanut allergenicity

Peanut allergy is a typical IgE-mediated immune disease. In susceptible individuals, upon peanut exposure, peanut-specific IgE (sIgE) bound to high-affinity IgE receptors primarily on mast cells and basophils successfully triggers cascade of inflammatory reaction and release of mediators, causing clinical symptoms. Peanut is the seed of an annual leguminous plant (*Arachis hypogaea* – Ara h) of family *Leguminosae*. The International Union of Immunological Societies Nomenclature subcommittee recognizes eight important allergenic proteins in peanuts, Ara h 1 to Ara h 8 [12]. The major peanut allergens are homologous to seed storage proteins of conglutinin, vicilin and glycinin family, except Ara h 5 (profilin) and Ara h 8 (pathogen-related peptide family related to pollen-associated food allergy). The physicochemical properties of these IgE-binding epitopes confer resistance to heat, digestive enzymes and food processing, contributing to increased allergenicity. High heat of roasting peanuts increases their allergenicity compared with boiling or frying [13]. The roasting process leads to Maillard reac-

tion or nonenzymatic glycosylation of amino groups, leading to stable glycosylated end-products and also increased IgE binding [14]. Although unproven, these cooking methods were thought to be responsible for global difference in peanut allergy. Better understanding of effects of food processing is required to elucidate its impact on food allergies, including development of peanut sensitivity and clinical reactions [15*].

Diagnosis

In clinical practice, diagnosis of peanut allergy is based on suggestive or uncontested history of immediate reaction after exposure (commonly oral) to peanut protein. Additional supportive tests like a positive skin prick test (SPT) with crude peanut extracts or serum sIgE is often necessary [16]. In the absence of reliable clinical history, detection of sIgE will not discriminate sensitized (clinically asymptomatic) from symptomatic or allergic patients [17]. As a result, many of these patients are subjected to oral food challenges for confirmation. Only double-blinded placebo-controlled peanut challenge tests (DBPCFC) are considered the gold standard for diagnosis [18]. However, this challenge is not always practical; it is time-consuming, expensive and fraught with risk of reactions and, therefore, used commonly in research settings. As an alternative to the basis of oral food challenges in high-risk children, various authors have published 'decision points' of quantitative food-specific IgE levels (milk, egg, soy, peanut and other) with 90 or 95% positive predictive values (PPVs) [19]. A sIgE more than 15 kUA/l (ImmunoCAP; Phadia AB, Uppsala, Sweden) [19] and/or SPT wheal size more than 8 mm suggests 95% likelihood of positive outcome on oral peanut challenge, thereby removing the need for risky food challenge [20]. Published studies report a wide range of sIgE from 5 to 57 kUA/l to indicate 100% PPV [21]. This difference is likely owing to study population, provocation protocol and focus of reactions. Detection of sIgE or SPT lacks specificity if used in isolation for diagnosis of peanut allergy, and lack of detectable sIgE is known to occur in patients with severe peanut reactions. Owing to these limitations, scientists are exploring other diagnostic tools like IgE epitope mapping and component-resolved diagnosis to characterize food sensitivities.

All eight peanut allergens express strong B-cell and T-cell-binding epitopes and elicit IgE antibody response. These peptides from peanut allergens like Ara h1, Ara h 2 and Ara h 3 have been used to define clinical reactivity patterns in peanut-allergic patients. Beyer *et al.* [22] also demonstrated difference in IgE-binding epitope recognition between peanut-tolerant and peanut-allergic patients, with the majority of allergic patients showing binding to three immunodominant epitopes of Ara h 2.

The authors suggested specific patterns of epitope recognition might provide prognostic information about peanut reactivity, including persistence. Other studies of milk, egg and wheat allergy also have shown a correlation between IgE sequential epitope diversity and patients' allergy severity and persistence [23]. An approach of component-resolved diagnostics correlating clinical symptoms against profile of IgE binding to panel of specific food allergens is increasingly studied. Several component-resolved diagnostic studies in food (soy, hazel nut) allergy suggest that using a panel of allergen molecules may define clinical information about severity or persistence of reaction. Using microarray assays that allow detection of sIgE to major peanut allergens (Ara h 1, 2, 3), grass allergens (Phl p1, 4, 5b, 7 and 12) and potentially cross-recognizing components [Bet v1, Pru p3 and cross-reacting carbohydrate determinant (CCD)], Nicolaou *et al.* [24^{••}] were able to detect a difference in pattern of component recognition between allergic and tolerant children in a small population of birth cohort of peanut-sensitized children. Patients with peanut allergy had higher response to Ara h 1–3, whereas tolerant patients had higher response to grass components and CCD. Authors suggested Ara h 2 appeared to be an important discriminating allergen for predicting clinical reactivity. Albrecht *et al.* [25] have questioned this approach of using epitopes to determine clinical sensitivity. IgE-binding peptides may be a diagnostic marker but not act as a full epitope to cause clinical reaction. Additional studies are necessary before this may have clinical applicability. It is indeed important to find useful tests that can distinguish clinical sensitivity and sensitization (asymptomatic) and be used as biomarkers in future.

Treatment

Currently, the only available treatment for peanut allergy is vigilant avoidance of peanut-containing foods and educating patients to recognize and treat acute reactions. Unfortunately, accidental reactions continue to recur. No curative therapy is available. Various immunomodulating approaches are investigated in animal models. Two therapies have generated immense interest: oral peanut immunotherapy and Chinese herbal medicine. Oral ingestion of food allergen results preferentially in active nonresponse to food antigen in normal individuals. Food allergy results from failure to develop or a breach in oral tolerance. Animal studies suggest two possible mechanisms of oral tolerance: a high-dose feeding of antigen results in anergy or deletion of antigen-specific T lymphocytes, whereas intermittent feeding with low dose is more likely to cause activation of regulatory T cells and release suppressive mediators [26]. Oral immunotherapy with other food antigens like milk, egg and sublingual hazel nut has shown temporary tolerance of higher doses of food antigens [27]. In an open-label study with intention

to treat 39 children with peanut allergy, Jones *et al.* [28^{••}] showed tolerance of 3.9 g of peanut protein in 27/29 participants who completed the study. Peanut was administered under observation in the initial phase (dose increased from 0.1 to 50 mg), followed by home incremental dosing of 25 mg every 2 weeks, until daily 300 mg during buildup phase was achieved. The 300 mg dose was continued in maintenance phase or the dose was increased to 1800 mg in some after oral peanut challenge. Mild reaction symptoms resolved spontaneously or with antihistamines. By 6 months, titrated SPTs and activation of basophils significantly declined. sIgE decreased in 12–18 months, whereas IgG4 increased significantly. Peripheral blood mononuclear assay showed increase in interleukin (IL)-5, IL-10, interferon-gamma (IFN- γ) and tumor necrosis factor-alpha (TNF- α) over 6–12 months. Peanut-specific T-regulatory cells increased until 12 months and decreased thereafter. This study indicated clinical efficacy of peanut oral immunotherapy and also changes in immune regulation. Analysis of safety of the home-based peanut immunotherapy protocol showed that risk of reaction with any home doses was 3.5%, usually mild skin or upper respiratory. Treatment was given only for 0.7% of home doses. Only 2/28 participants received epinephrine [29[•]]. A continued evaluation of reactions with home doses of peanut proteins during oral therapy suggested concurrent illness, doses not mixed with other food as recommended, suboptimal asthma control, physical exertion after doses or dosing during menses are likely risk factors for reactions [30[•]]. This study will lead to more oral immunotherapy (OIT) trials and, therefore, real-world information that will benefit clinicians. Other studies also demonstrate change in the threshold dose of food antigen needed to cause allergic reaction or desensitization while the food antigen is regularly eaten. The development of tolerance or long-term immunologic changes allowing ingestion of culprit food antigen without symptoms and with interruptions is not proven. Nevertheless, an increased threshold dose of food antigen provoking reactions creates a safety net for peanut-allergic individuals. Future studies with regard to patient safety, acceptable dosing, efficacy, predictive factors for clinical reactions and long-term tolerance have to be established before peanut oral immunotherapy is used in clinical practice.

Chinese herbal medicine is a promising option among various immunomodulatory approaches studied in animal models. Using refined food allergy herbal formula 2 (FAHF-2) containing nine herb extracts, Qu *et al.* [31] were able to completely block peanut-induced anaphylaxis in a mouse model when the extract was administered intragastrically during the development of peanut hypersensitivity (early treatment) and also after peanut hypersensitivity was fully established (late-treatment protocol) [32]. The protection was associated with

suppression of histamine release and T-helper cells (TH2) responses (IgE and TH2 cytokines) and upregulation of T-helper cells (TH1) responses (IgG2 and IFN- γ). After approval for investigational new drug (IND) from Food and Drug Administration (FDA) and local institutional review board, a FAHF-2 clinical trial was initiated in 2008. A double-blind, dose-escalation phase I study was conducted on 12 participants (eight FAHF-2 and four placebo) with peanut and other food allergies. The result showed that FAHF-2 is safe and well tolerated, and an extended open-label study will be investigated [33^{*}]. Although FAHF-2 showed efficacy and safety in an animal model of peanut anaphylaxis, issues regarding mechanism of action, active ingredients, quality control, side-effects and human data need to be explored.

Peanut allergy management

Until new treatment options become available, current treatment includes educating patients and their families about reading food labels, avoiding peanut, avoiding high-risk foods like ethnic, ice-cream toppings, unlabeled desserts, and candies, and also informing all care takers, school and others about severity of reactions. All patients should be taught about recognizing early-reaction symptoms and have a written acute care or anaphylaxis action plan. The written plan should include appropriate instructions and prescription for intramuscular auto-injector epinephrine, antihistamine like diphenhydramine and perhaps oral steroid (if necessary). The patient should be instructed to proceed to the nearest emergency medical facility, particularly after severe peanut reactions.

Conclusion

Interesting new strategies are being investigated in research settings with a hope of well tolerated treatment for peanut allergies in future. The current advances continue to provide new insights into peanut allergies.

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

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 683–684).

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