

Allergic Reaction to Peanuts: Can We Predict Reaction Severity in the Wild?

Aisling Flinn · Jonathan O'B Hourihane

Published online: 7 July 2013
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Abstract Peanut allergy (PNA) is the main cause of food-induced anaphylaxis. Severe allergic reactions are more likely to occur in older patients and those with underlying asthma. Skin prick testing and measuring serum-specific IgE and recombinant peanut protein levels have been shown to be useful in the diagnosis of PNA and prediction of reactivity, but these tests are less consistent and reliable in terms of predicting the severity of reactions. Recent research has examined the role of biological mediators in allergic reactions such as platelet-activating factor. These may provide a future tool in predicting those at risk of severe reactions. Currently, there are no parameters that can predict with certainty those at risk of anaphylaxis, and management of PNA should continue to focus on patient and family education.

Keywords Peanut allergy · Severity · Reaction · Allergic reaction · Anaphylaxis · Asthma · Skinprick testing · Peanut-specific IgE · Recombinant peanut protein · Predict · Atopic diseases · Biological mediators

Introduction

Peanut allergy (PNA) affects approximately 1 % of children and 0.6 % of adults [1]. Sensitization to peanut occurs in approximately 3 % of the population [2], increasing to 5 % in those with a history of atopy [3]. Reactions are often severe, occasionally fatal, and the condition is usually lifelong. Diagnosis can be made by a combination of a detailed medical history, skin prick testing, measuring levels of serum

peanut-specific IgE antibodies, and, more recently, recombinant proteins, but the gold standard for diagnosis is a double-blind, placebo-controlled food challenge (DBPCFC). The prevalence of PNA appears to be increasing in the developed world [4]. In tandem with the increased prevalence of PNA, hospitalization rates for peanut-induced anaphylaxis have also increased [5]. The current mainstay for management of PNA is strict allergen avoidance. Oral immunotherapy (OIT) has become a hot and contentious topic of both research and public debate as a potential way of transforming the future management of PNA. The aim of OIT is to induce desensitization followed by tolerance to peanut, but at present there is still uncertainty about its safety and efficacy, and hence its use is currently only recommended in the setting of clinical trials [6].

PNA is responsible for the majority of cases of food-induced anaphylaxis and is associated with more severe symptoms than other food allergies. Exposure to even traces of peanut protein in susceptible sensitized individuals can lead to a fatal reaction. The majority of fatal cases of anaphylaxis have a known allergy prior to the fatal event [7]. Older patients tend to suffer from more severe allergic symptoms than children [8, 9]. More significant allergic reactions tend to occur in the community, and so there are likely to be other contributing factors at play such as exercise and alcohol consumption. If a higher-risk group of patients were identifiable, they could be particularly targeted in terms of education and surveillance.

Coexisting Atopic Diseases

Respiratory arrest is the most common mechanism behind fatal cases of anaphylaxis in children [10], thus leading to the theory that in patients with food allergy, underlying airway hyper-reactivity and inflammation is associated with a higher risk of severe reaction or anaphylaxis. Calvani et al., in a

A. Flinn · J. O. Hourihane (✉)
Department of Pediatrics, Cork University Hospital, Cork, Ireland
e-mail: J.Hourihane@ucc.ie

A. Flinn
e-mail: flinna@tcd.ie

prospective study of 163 children with food allergies, showed that a clinical history of asthma increased the risk of wheezing [odds ratio (OR) 2.2; 95 % confidence interval (CI) 1.1–4.5] and respiratory arrest (OR 6.9; 95 % CI 1.4–34.2) [11]. Colver et al. similarly showed that asthma was a strongly significant risk factor for severe allergic reactions to food (not specifically to peanut although peanut was the main allergen described) [12]. In a questionnaire study of 622 patients with self-reported PNA, those with a history of asthma were more likely to have severe symptoms [8]. Summers et al., in a study of 1,094 patients with tree nut and peanut allergies, demonstrated that, as well as severe asthma being associated with life-threatening bronchospasm, severe pharyngeal edema was more common in patients with severe rhinitis. They also found that having severe eczema was associated with a 3-fold risk of becoming unconscious during an acute allergic reaction, thus further highlighting the link between the severity of acute allergic reactions and the severity of co-existing atopic disease [9].

Reports on fatal or near-fatal cases of anaphylaxis can provide important information with regard to triggers or aggravating factors. In a small series of 13 cases of fatal or near-fatal anaphylaxis to food, all patients had a history of asthma [13]. Bock et al. reported similar findings among 32 fatal cases; all but 1, (for those who had a history available) had a history of asthma [7].

FeNO (fraction of expired nitric oxide) is a non-invasive marker of eosinophilic airway inflammation and has been shown to be elevated in those with poorly controlled asthma. Asthmatic children with food allergies have been shown to have significantly higher eosinophil sputum counts and FeNO than those without food allergies [14]. Hughes et al. looked at the levels of FeNO in peanut-allergic patients [15]. They found that children who had outgrown their asthma had elevated FeNO levels, suggesting persisting eosinophilic airway inflammation, although the number of patients was small ($n=7$). Thus, adolescents who no longer have asthma symptoms clinically may still have ongoing airway inflammation and instability, which may help explain why they tend to exhibit more severe allergic symptoms.

History of Anaphylaxis/Severity of Previous Reaction

Some studies have previously suggested a relationship between a history of anaphylaxis or severe symptoms and the risk of anaphylaxis upon subsequent exposure [8, 16], but others have found contradictory results. Wainstein et al. looked at a group of 21 children who reacted with anaphylaxis following oral food challenges and found that a history of anaphylaxis was not predictive of anaphylaxis on challenge [17•]. Flinterman et al. also found no association between the severity of reaction in the history and severity

of reaction during DBPCFC or with the eliciting dose [18], and we have previously documented that a poor correlation exists between the reported reactions in the community and the reaction elicited in low-dose DBPCFC. There was, however, a weak correlation between the most recent reaction in the community and the challenge reaction [19].

Peanut-Specific IgE: In Vivo and in Vitro Testing

Skin prick testing (SPT) and serum peanut-specific IgE levels are important tools in the diagnosis of peanut allergy. Both have been shown to be useful in predicting the likelihood of eliciting a clinical reaction. Johannsen et al. showed that for predicting a positive oral challenge outcome when combining a SPT result of >7 mm with specific IgE >2 kU/L, the sensitivity was 96 % and the negative predictive value 95 % [20]. Many other studies have been carried out examining the relationship between SPT and serum peanut-specific IgE levels and the outcome of oral food challenges. Overall, results have shown that higher specific IgE concentrations and larger wheal sizes are associated with a higher risk of a clinical reaction [20–23]. However, opinions are more conflicting regarding the use of in vivo and in vitro peanut-specific IgE in predicting the severity of clinical reactivity.

Some studies have shown a positive correlation between peanut-specific IgE and clinical severity [24]. Wainstein et al. looked at a group of 21 children who developed anaphylaxis following oral food challenge. They found that, compared to the control group, the study group had significantly higher median specific IgE levels (19 kU/l compared with 0.68 kU/l, $p<0.0001$) and significantly larger mean SPT wheal size (10.2 mm compared to 6.7 mm, $p<0.0001$). In terms of predicting anaphylaxis, they found that a SPT wheal size of 11.25 mm was 33 % sensitive and 97 % specific. A peanut-specific IgE level of 7.7 kU/l was 70 % sensitive and 97 % specific [17•].

The association between higher levels of peanut-specific IgE and reaction severity was also found by Neuman-Sunshine et al. in a study of 782 patients with persistent peanut allergy. Serum peanut-specific IgE >24.8 – 99.9 kU/L had an odds ratio of 2.0 and >100 kU/L had an odds ratio of 3.3 for severe reactions compared with having an initial peanut-specific IgE <4.8 kU/L [25]. They found no association between reaction severity and age, sex, or asthma.

We have shown in a prospective study of 40 children that there was an association between peanut-specific IgE levels and clinical reactivity in DBPCFCs. The association between peanut-specific IgE with challenge outcome was stronger in those without asthma, which suggests that the presence of asthma and its negative influence on outcome in the community is more important than the levels of peanut-specific

IgE in isolation. This further supports our view that no single feature of the history or in testing can be used as a solo biomarker of future severity of peanut allergy [19].

Van der Zee et al. demonstrated that greater clinical sensitivity to peanut, defined by the eliciting dose in DBPCFCs to peanut, was found to be associated with increasing age, higher specific IgE level, and the absence of atopic dermatitis [26]. This finding may help to explain why adolescents experience severe allergic reactions to peanut more often than younger children.

Conversely, other studies have not found any relationship between peanut-specific IgE levels and the severity of clinical reactions. Rancé et al. reported no significant association between SPT or specific IgE concentrations and the severity of reactions [27]. In a group of 27 peanut-sensitized children, Flinterman et al. showed that, although the severity of the reaction during DBPCFC was weakly correlated to SPT reactivity ($p=0.49$; $p=0.021$), it did not correlate with specific IgE levels [18]. Similar findings have been reported by Clark [28], Summers [9], and Von Ta et al. [29].

However, despite some studies showing a correlation between higher levels of peanut-specific IgE and clinical severity, severe and life-threatening reactions have been shown to occur at all levels of peanut-specific IgE concentrations, and it is apparent that reactivity during a controlled hospital-based exposure during oral food challenge is not a robust predictor of reactivity in the community, when multiple other factors are operative.

Recombinant Peanut Proteins

Peanuts are comprised of many different proteins. Recent studies have been carried out looking at the diagnostic value of these recombinant peanut allergens. Ara h 1 (vicilin), 2 (conglutin), and 3 (glycinin) are heat-stable seed-storage proteins and are considered to be the major peanut allergens contributing to peanut sensitization. Ara h 4 is an isoform of Ara h 3 and Ara h 6 is homologous to Ara h 2. With the development of component testing, further knowledge has been acquired with regard to predicting clinical severity.

Movérare et al. showed, in a study of Swedish patients with peanut allergy, that severe reactions with symptoms of respiratory distress were associated with sensitization to Ara h 1, 2, or 3 (56 % of patients sensitized to Ara h 1–3 compared to 18 % of patients not sensitized to Ara h 1–3), $p<0.01$ [30]. Two cases of anaphylaxis were reported among the individuals sensitized to Ara h 1–3.

Peeters et al. looked at whether sensitization to Ara h 1, 2, 3, or 6 can predict the severity of allergic reactions to peanut in a group of 30 patients. They found that patients with severe reactions had a higher SPT response to Ara h 2 and

Ara h 6 at low concentrations and to Ara h 1 and Ara h 3 at higher concentrations. They also found that patients with more severe symptoms recognized a greater number of allergens [31].

Astier et al. looked at the diagnostic value of the three major peanut recombinant allergens, Ara h 1, 2, and 3. All patients with positive SPT were sensitized to Ara h 2, and 53 % were sensitized to Ara h 2 alone. However, patients with monosensitization to Ara h 2 had a significantly lower severity score than polysensitized patients [32]. Sensitization to Ara h 2 plus sensitization to Ara h 1 and/or Ara h 3 was associated with greater severity of reactions. Peptide microarray immunoassays in a group of 77 patients similarly showed that those with wide epitope diversity were associated with a history of more severe allergic reactions [33].

These findings, along with others such as by Lewis et al. [24], further strengthen the theory that a wide diversity of IgE binding is important in predicting clinical severity of reactions, and, although further research is needed, better prognostic tests may be available in the future using peptide microarray immunoassays.

Biological Mediators

Biological mediators in anaphylaxis are the targets of more recent research, and biomarker panels may provide a role in the future of diagnosis, management, and prevention of severe allergic reactions.

Anaphylaxis is a clinical diagnosis with no laboratory tests currently available for confirmation. Serum tryptase levels (when taken within a few hours after the onset of symptoms of anaphylaxis and particularly serial measurements) and mast cell carboxypeptidase A3 have been reported in some studies to be useful in the diagnosis of anaphylaxis [34]. However, tryptase levels appear to be less consistently elevated in food-induced anaphylaxis, thus making it less valuable in this domain [13]. It has been suggested that measuring a panel of mast cell and basophil mediators may be helpful in diagnosis of anaphylaxis, but it is unclear at this time how useful they would be in risk assessment.

Platelet-activating factor (PAF) is a pro-inflammatory phospholipid produced by mast cell, monocytes, and fixed tissue macrophages. Levels of PAF are controlled by the enzyme PAF acetylhydrolase which hydrolyzes PAF to its inactive form. Animal studies have shown that PAF antagonists or deactivation protect against anaphylaxis. Vadas et al. looked at the role PAF and PAF acetylhydrolase activity in acute allergic reactions and found that PAF levels were increased and PAF acetylhydrolase activity was decreased in proportion to the severity of acute allergic reactions [35]. They also showed that acetylhydrolase activity

was significantly lower in nine patients with fatal peanut anaphylaxis compared to those with mild allergic reactions to peanuts and in the control group. PAF levels also appear to correlate better with severity of allergic reactions compared to histamine and tryptase levels. Although PAF does not act in isolation in predisposing to severe allergic reactions, it may provide a potential future target for treatment.

Angiotensin-II is a potent vasoconstrictor, produced by the action of angiotensin-converting enzyme (ACE) in response to vasodilation. ACE also plays a role in the catabolism of bradykinin, which is a potent vasodilator and plays a pivotal role in increasing vascular permeability and angioedema. In a study of patients who had peanut or tree nut allergic reactions, 122 patients had serum aminopeptidase P (APP) and ACE levels measured, both important mediators in the breakdown of bradykinin. Low levels of ACE were associated with severe pharyngeal edema but not with severe bronchospasm, reduced consciousness, and urticaria. Serum APP concentrations did not vary significantly with severity of allergy symptoms [9]. Varney et al. looked at serum ACE levels and genotypes in patients with food, drug, or venom allergies. They found that airway edema and cardiovascular collapse was more likely to occur in those with the 'I' genotype, with its associated reduced ACE activity and reduced bradykinin catabolism. Similarly to Summers et al., they also showed that levels of ACE were lower in patients who experienced symptoms of airway edema and cardiovascular collapse [36].

Studies with murine models have looked at the role of the innate immune system in anaphylaxis. Khodoun et al. showed that peanut extract stimulates the activation of complement, with the production of C3a, which activates basophils, macrophages, and mast cells, releasing platelet-activating factor and histamine, contributing to the development of shock [37]. Further work by Kodama et al. demonstrated that complement activation by peanut extract acts via the lectin and classical pathways in vivo [38]. Maltby et al. showed that loss of IL-7R α and L-selectin in mice, both important molecules in the adaptive immune response, reduced the severity of peanut-induced anaphylaxis and suggested that future interventions aimed at the initial immune sensitization to peanut may be successful [39].

Conclusions

At present, there are no completely reliable parameters available to predict the potential severity of an allergic reaction to peanut. Co-existing asthma does appear to be an important associated, but not predictive, factor in severe allergic reactions, and no single parameter should be used as a tool to predict the severity of future clinical reactions. Trying to predict which patients are at high risk of peanut anaphylaxis

may be a Sisyphean task, a pursuit to answer a question that cannot be answered with certainty. The evidence for and against in vivo and in vitro peanut-specific IgE remains disparate as a means to predict reaction severity. Further understanding of the recombinant peanut proteins and diversity of binding may, in the future, be a useful prognostic aid, but further research is needed. Patients with peanut allergy remain at risk of a severe or fatal reaction despite having none of the risk factors listed. What is important is that patients, their families, and medical professionals understand the lack of prognostic certainty, so that each patient is prepared for a severe reaction or anaphylaxis at all times. Attending a specialist allergy clinic, and the development of a comprehensive management plan, has been shown to result in less frequent and less severe subsequent reactions, thus further emphasizing the importance of education as the cornerstone of management [40, 41].

Bock et al.'s series of 32 fatal cases of anaphylaxis showed that most of these individuals did not have epinephrine available at the time of their fatal reaction [14]. Other studies similarly indicate that many severe allergic reactions are inadequately treated [9, 16]. In a study of 110 families who had been prescribed epinephrine pens, only 55 % carried unexpired epinephrine at the time of the study and only 32 % were able to correctly demonstrate how to use the device [42]. Patients must be educated on how to recognize early symptoms of an allergic reaction, management of an anaphylactic reaction, including the need to carry at all times and safely administer self-injectable epinephrine, as well as having appropriate medical identification. This must be done for every patient regardless of the aforementioned parameters.

Improved understanding of the pathophysiology of anaphylaxis has led to new research exploring ways of trying to differentiate individuals at low or no risk of severe reactions and those with a high risk. Tools such as peptide microarray immunoassays may help us in risk assessment in the future, but until then prevention of anaphylaxis is paramount, concentrating equally on patient education, strict avoidance of peanut, and preparedness to self treat with epinephrine.

Compliance with Ethics Guidelines

Conflict of Interest Jonathan O'B Hourihane has received grant support from the Food Standards Agency UK, the National Children's Research Centre Ireland, and Danone; has received speaker fee honoraria from Mead Johnson, Nutricia, and Pfizer; and has had travel/accommodations expenses covered/reimbursed by Stallergenes and Nutricia.

Aisling Flinn declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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