

REVIEW

Peanut allergy

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Introduction

Food allergy is an uncommon but definite clinical entity [1,2]. Since its early description by Prausnitz and Kustner in 1921 [3], clinical acceptance of food sensitivity has been delayed by the lack of laboratory tests despite the clear clinical history described by the patients. However, since that time multiple studies have fully validated the existence of various food sensitivity syndromes [4,5] including anaphylaxis [6,7]. The majority of allergic reactions to foods are believed to be IgE-mediated, mast-cell dependent immediate hypersensitivity reactions [8], although other mechanisms can be involved such as immune complex formation [9–11], complement deposition [12], and cell-mediated immune reactions [13,14].

Prevalence of food allergy

The true prevalence of immediate food-hypersensitivity reactions in the paediatric and adult populations is not known. It is clear that many people die each year from allergic reactions to food, but the actual mortality rate is not known either. This is due to the diagnostic problems with anaphylactic deaths and actual death certification. Complacency on the part of the medical community, largely resulting from the plethora of inaccurate information on the subject, has contributed to this dearth of information [15]. It is generally accepted that the prevalence is higher in children with figures in the range of 0.3–7.5% [16], than in adults [17,18]. In the paediatric group it is more common in atopic subjects [19–21]. In children, food hypersensitivity can be a transient phenomenon but may predict later sensitization to inhalent allergens [4,22–24].

Prevalence of peanut allergy

Peanuts are one of the most common foods causing allergic reactions both in children and adults [19,25–30] and its involvement in food allergic reactions seems to have increased in the past decade [31]. In 81 children and adolescents aged between 3 and 16 years with a history of

food associated allergy, May and Bock [32] diagnosed 17 (21%) of these patients as being allergic to peanuts using double-blind food challenges. Similar observations were made by Aas [33]. Peanuts were also found to be one of the few foods eliciting hypersensitivity reactions in infants under 3 years of age. Atopic infants have an increased risk of developing sensitization to peanut [56] with some studies finding a prevalence rate ranging from 10% [34,35] to 68% [36], which seems rather high. The possibility of genetic transmission of peanut allergy has also been suggested [37]. Unlike many other food allergies, peanut allergy is rarely outgrown [6,19,37–39].

Botany

Peanut (*Arachia hypogea*) is a member of the prolific legume family and closely related to peas and beans, a wide variety of which are commonly eaten. Other members of the legume family are peas, beans, soy beans, kidney beans, garbanzo beans, carob beans, clover lupines and lentils. The plant is a bushy annual with colourful yellow flowers. The flower stalk elongates greatly after fertilization has taken place, the weight causing it to bend downward until the ovary has been pushed into the ground. It is in the ground that the familiar peanut develops and harvesting requires digging [40].

Use and consumption

Excavations in South America indicate that peanuts of the genus *Arachia* were already cultivated 2000–3000 BC [41]. During the last decades demand for peanuts has steadily increased because of their value as a source of easily digested protein [42] and their versatility. They can be eaten as a vegetable, crushed or ground as a 'butter', roasted or salted as snacks, incorporated into candy and used as an oil extracted by solvents or pressure. The credit for developing the many uses for peanuts goes to George Washington Carver. This American biochemist was interested in enriching the diet of the poor minorities of his day. In order to create employment for them, he also introduced the use of peanut into the manufacture of such disparate products as plastics, linoleum, adhesives, bleaches and shampoos [43].

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In the United States, which is one of the world's largest producers of peanuts, one half of the peanut crop is consumed as peanut butter, 20% sold for use as table peanuts, 16% is used in candy and baked goods and the remainder processed into oil [41].

Chemistry

Peanut kernels contain approximately 45–50% oil, 25–30% protein, 8–12% carbohydrate, 5% water, 3% fibre and 2.5% ash [44]. The peanut skin contains 49% carbohydrate and 19% fibre [42] along with tannins and pigments which cause undesirable colours in peanut products unless removed during the initial processing [45].

Peanut proteins were originally classified as albumins (water soluble) or globulins (saline soluble); the globulins were in turn subdivided into arachin and conarachin fractions (the major storage proteins) [46–48]. Native arachin in the seed has a molecular weight of at least 600 kDa [44], but readily disassociates into arachin, with a dimer molecular weight of 330 kDa and a monomer of 170 kDa [49,50]. There are two polymorphic forms of arachin, A and B [51]; arachin A has α , β , γ and δ chains, while arachin B lacks the α chain. By sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE), arachin can be dissociated into a variable number of subunits varying from 10 to 71 kDa [52,53].

Conarachin can be separated by ultracentrifugation into 7.8 S and 12.6S components, with a calculated molecular weight of 142 and 295 kDa respectively [54,55]. The latter component is designated as conarachin II or alpha conarachin. By SDS-PAGE, conarachin II can be dissociated into multiple subunits having molecular weights ranging from 18 to 62 kDa [56].

Other components of the albumin fraction of peanuts are agglutinins [57], lectin-reactive glycoproteins [58], protease inhibitors, alpha-amylase inhibitors and phospholipases [59].

Allergens

A significant body of work has been done to identify and purify inhalent allergens from a wide variety of sources including pollens, dust mites, animal danders, insects and fungi [60]. In comparison, very little work has been completed on food allergens that are known to cause IgE-mediated reactions [61–63].

Peanut allergens (Table 1) are relatively heat stable and are thus present in both raw and roasted peanuts [64–68]. Chemical denaturation of peanut proteins, as when treated with enzymes in the immobilized digestive enzyme assay system used to mimic human digestion, appears only to reduce minimally the IgE and IgG specific binding [64], perhaps indicating that the allergic epitope is a linear peptide.

Early attempts were made to isolate peanut allergens by Spies *et al.* using ethanol fractionation and basic lead acetate precipitation [69]. Subsequently, a major peanut allergen designated 'Peanut I' was isolated by Sachs *et al.* from raw, defatted, peanut meal extract [70]. By thin layer isoelectric focussing, Peanut I contained bands with pI ranging from 5.25 to 5.75. By SDS-PAGE there were two major bands with apparent molecular weights of 20 and 30 kDa. Peanut I was biologically active as demonstrated by positive skin tests and leucocyte histamine release assays in patients with peanut allergy. These investigators concluded that Peanut I is an acidic glycoprotein with non-identical subunits. However, by RAST inhibition assays, there was a suggestion that this protein did not account for all the allergenic potential of peanuts.

Using RAST assays, Australian investigators have examined the allergenicity of the major components of peanut, namely, α -arachin, conarachin I, the concanavalin A-reactive glycoprotein, peanut agglutinin and peanut phospholipase D [67]. All test sera contained IgE antibodies to α -arachin and conarachin I, but fewer sera reacted with peanut agglutinin and phospholipase D. The allergenicity of the concanavalin A-reactive

Table 1. Peanut allergens

	pI	Mol. wt.
Peanut I (Sachs <i>et al.</i> 1981) [70]	5.25–5.75	20–30 kDa
Con A-reactive Glyc. (Barnett <i>et al.</i> 1986) [71]	4.6	65 kDa
(Meier-Davis <i>et al.</i> 1987) [74]	—	15 kDa
Ara hI (Burks <i>et al.</i> 1991) [72]	4.55	63.5 kDa
Ara hII (Burks <i>et al.</i> 1992) [64]	5.2	17 kDa

pI, isoelectric point. Mol. wt. molecular weight.

glycoprotein was confirmed in subsequent skin test experiments [71]. The concanavalin A-reactive glycoprotein has a monomeric molecular weight of 65 kDa and a pI of 4.6.

Burks *et al.* [30,72] purified two fractions from crude peanut extracts which were called *Ara hI* and *Ara hII* by the Allergen Nomenclature Committee of the IUIS. By PAS staining, these protein bands were found to be glycoproteins with a pI and a molecular weight of 4.55 and 63 kDa and 5.2 and 17 kDa respectively. For their identification, many techniques were used; SDS-PAGE, ELISA-inhibition, thin layer isoelectric focussing, amino acid analysis, sequencing, carbohydrate analysis and two-dimensional gels. The authors noted the similarity between *Ara hI* and the Con A-reactive glycoprotein described by Barnett *et al.* [73], as well as the similarity between *Ara hII* and one of the allergenic fractions identified by Meier-Davis *et al.* [74].

Sensitization

As with other IgE-mediated diseases, prior exposure and sensitization to food allergens usually precede the initial anaphylactic reaction. However, there have been reports of anaphylaxis occurring on the first known exposure to a food substance [36,38,75–78] including peanuts [37,38,79] indicating that sensitization had occurred *in utero*, through breastfeeding or through an unknown route of exposure. Although suspected *in utero* sensitization has been reported [80–82], only Kaufman [83] demonstrated an IgE-mediated reaction at birth. It seems that *in utero* sensitization is less important than previously believed [84].

The presence of food allergens in breast milk was described early this century [85–87] and includes the classic studies of Donnally [88] who used breast milk from mothers who had eaten egg to show skin-test positivity in patients who were allergic to egg. Subsequent studies confirmed these findings [76,81,82,89–94]. Peanut protein has also been detected in breast milk [4,31,38,95]. Sensitization may occur through traces of proteins in peanut oil that are contained in some infant formulae [96,97] and in Vitamin D preparations [98].

Inadvertant exposure

Peanut sensitization by unknown exposure is an ever more frequent possibility due to the ever more inconspicuous use of peanuts or peanut butter in candies, biscuits, pastry, chilli and Chinese egg rolls. Some oriental restaurants use peanut butter to 'glue down' the ends of egg rolls to stop them coming apart in the

cooking process. Peanut butter also has the desirable ability, from a cooking point of view, to make soft foods more firm [78]. Problems have arisen with contamination of foods during the manufacturing process, especially in processing plants where there is a production switch-over from one product to another.

A reaction to almond butter by a peanut allergic individual led to an investigation that found 10% of almond butter produced by a given plant was contaminated with peanut protein. This resulted from the production switch-over from peanut butter to almond butter [95]. The same problem has occurred with candy manufacturers when candies with and without peanuts were prepared by the same machines.

To compound this problem, new food products containing peanut allergens are being introduced. Deflavoured peanuts are another unusual example [68]. These are peanuts that have been pressed, deflavoured, re flavoured and sold as other nuts such as walnuts or almonds! This form of processing presents a very serious potential risk to peanut allergic subjects. Finally, the possibility of food sensitization through exposure to inhalent allergens has been reported [99], presenting as the 'Oral Allergy Syndrome'. With specific respect to peanut, the cluster is seen in subjects monosensitized to grass pollen, but also reacting to tomato and peanut [100].

Relationship between peanut and tree nut allergy

It is frequently said that if a patient is allergic to peanuts, they are no more likely to be allergic to tree nuts (hazel, almond, walnut etc.) than any other person with an allergy. This is not the case. After the five deaths from peanut anaphylaxis that occurred in 1993, a charity called the 'Anaphylaxis Campaign' was formed to help patients in the UK and worldwide who have had an anaphylactic attack. Information from a questionnaire from 1250 patients who have had anaphylaxis from peanuts has now been obtained. Although only 10% of the patients have been seen personally (by Dr A. W. Frankland and J. Brostoff), the questions have been accurately answered and are ready for full analysis.

The preliminary results from the first 791 peanut allergic patients show that 35.4% considered that peanuts alone caused trouble. A further 18.2% who were mostly under the age of 2 years had not eaten any other nut product so were classified a 'don't know' or 'not sure'. This means that approximately 50% of people with peanut allergy are also allergic to other nuts. In all, 14 different nuts caused allergic reactions but peanuts caused as many reactions as all the other nuts combined. There is little data in the literature concerning this point so this finding represents the most up-to-date percentage

in these patients. Of note is that one-third of this group had been admitted to hospital for emergency treatment.

Anaphylaxis

Peanut seems to be the most likely food to cause anaphylaxis. In reports of fatal reactions to food, peanut was the cause in the majority of them [6,7]. A study of emergency departments has shown that one-third of all patients admitted to hospital with anaphylactic reactions were due to peanut [101].

Clinical features

Peanuts are one of the most allergenic foods [102,103] with acute and dramatic reactions. There are thus many case reports available describing the clinical characteristics of the allergic response [6,7,36,90,104]. It must be noted that not all of the reactions are due to ingestion of peanut, as injection, contact [37] and even inhalation [37,79] can produce symptoms. Symptoms include asphyxia with swelling of the upper larynx, epiglottis and tongue, urticaria, angioedema, asthma, rhinitis, eczema, mouth ulcers, nausea, pruritus, diarrhoea, cerebral involvement, and collapse including cardiac arrest and death [19,36,90,105,106].

Onset of clinical symptoms

The interval between food ingestion and the allergic reaction may vary from minutes to even hours. The first symptoms are often noticed in the mouth with a sensation of burning, irritation or itching in the lips, mouth and throat. This may provide the person with an immediate warning that they have eaten an allergenic food. Some children lick a suspect food to give themselves that early warning. Following this the patient may feel generally unwell, warm and develop generalized itching, faintness and sneezing. Fear is a prominent emotion at this stage. In severe cases, these early symptoms are followed in seconds or minutes by loss of consciousness and suffocation. Major causes of death in anaphylactic shock are due to obstruction of the upper airway (larynx and epiglottis) and heart failure. Death can occur within minutes of ingestion of the food.

Asthma and peanut allergy

A special relationship exists between asthma and severe reactions to foods which became apparent when analysing reported cases of anaphylaxis to peanuts [78]. Of the anaphylactic deaths reported up to 1992, six of the seven had a past history of asthma [6,95]. The recent study of Sampson *et al.* [7] of fatal and near fatal

anaphylactic reactions to foods adds to this conclusion, since all the patients described had a past history of asthma. In the United Kingdom, five out of the seven recent deaths from peanut allergy have also been in patients with a history of asthma (Anaphylaxis Campaign, personal communication).

It is clear that asthmatic subjects who experience acute anaphylaxis are more likely to have a severe reaction. This might be explained by the exquisite sensitivity of asthmatic lungs for endogenous mediators such as histamine, leukotrienes and prostaglandins produced by the acute food allergic reaction [78].

Exacerbating factors

These may be classified into factors that may make the allergic reaction itself more severe and the factors involved in eating away from home. The clinical reaction to peanuts can be hastened following alcohol ingestion [107], the taking of aspirin [108,109] and exercise [110–113]. The first two of these particular factors increase gut permeability and the last increases blood flow generally in the body.

From what has been said above, it is clear that peanut can be hidden in a variety of foods in disguised forms making it very difficult to avoid the allergen. One fact that is clear from the literature is that most fatal and near fatal reactions happen when eating away from home [6,7,37,39,68,109,114]. This is exemplified by the case of the student who died of peanut anaphylaxis after ingesting only two 'bites' of chilli that was adulterated with peanut butter [6]. These sad instances could be avoided if the peanut content of foods served by caterers and restaurants had to be identified [68,78,109,114,115].

Diagnosis

The diagnosis is based on the clinical history, demonstration of an IgE-mediated allergic mechanism and, if absolutely crucial, food challenge.

Clinical history

The history alone is reliable if there has been a major immediate anaphylactic reaction [28,34,90,116]. By the time the patient reaches a specialist clinic there may have been two or three further inadvertent challenges confirming the specific clinical sensitivity.

Skin tests

Skin tests by the skin-prick method are recommended by

the European Academy of Allergology and Clinical Immunology because of their safety and reliability [117]. They are more reliable in children than in adults [118] and their value obviously depends on the quality of the allergen extract. With peanut, they are positive in 50–70% of patients presenting with a confirmed allergic reaction [29,33,36].

Skin-prick tests are sensitive and have excellent predictive negative value, but have poor specificity and positive predictive value [90,119]. It is important to emphasize that a positive skin-test reaction (properly performed) merely indicates the presence of antigen specific IgE bound to cutaneous mast cells, i.e. immunological sensitization. The clinical significance of the positive skin test reaction can only be ascertained by other means, namely food challenge [8,26,36,119].

Dangers of skin tests and crossreaction with other legumes

Anaphylactic reactions to food extracts have been reported using the scratch technique [120] leading to some reluctance to perform skin-prick testing on patients with a history of anaphylaxis to food [37,121]. The lack of reliability of skin tests in pin-pointing specific food allergic reactions can be shown by oral challenge. Fourteen children with a convincing history of severe peanut-induced anaphylaxis were all skin-prick tested with peanut allergen, and all the children received oral challenges with other legumes [122]. All the 14 children had markedly positive peanut skin-prick tests and yet none experienced any serious untoward reaction after skin testing or oral challenge with other legumes [153]. In spite of this, it is wise to dilute the food extract prior to skin testing as to proceed cautiously [78].

In a further study of 113 children with atopic dermatitis, Sampson *et al.* [19] found that many children had positive skin-prick test reactions to several members of a botanical family, e.g. legumes; peanut, soyabean, green bean, pea. However, no child allergic to peanut reacted clinically to any other member of the legume family tested. The conclusion is that clinical reactions appear to be specific to individual food antigens, whereas skin-test sensitivity (as demonstrated by positive skin-prick test results) reflects some common antigen among members of a botanical family. Thus, clinical hypersensitivity to one legume does not warrant dietary elimination of the entire legume family unless hypersensitivity to each allergen is individually confirmed [122].

Laboratory tests

Among the many laboratory tests that have been used for the diagnosis of food allergy in general (Table 2)

[123], the most common and clinically well established is the RAST. Various reports comparing RAST with clinical food allergy cite false-positive RAST rates of 3–40% and false-negative rates of 3–48% depending critically on how the diagnosis of food hypersensitivity was ascertained [27,33,35,124–126]. Aas noted that diagnostic reliability varied considerably with the food antigen in question, being better for peanut allergen [33].

The RAST is less sensitive than direct skin testing and more expensive [34,118] and it has been suggested that it should generally be reserved for the rare patient with dermographism, the patient with severe skin disease or for those who cannot discontinue antihistamines [119]. This may be the best academic advice but a positive RAST in conjunction with a positive skin test is very supportive both for the doctor and the patient; the latter who may have to face a lifetime of avoidance of a single pervasive food allergen.

Food challenge

Various studies have confirmed the value of food challenge as the 'gold standard' for diagnosing immediate food hypersensitivity [90,119,126,127]. It has been rightly suggested that for a number of situations where food sensitivity is suspected, the best method of confirmation is the double-blind placebo-controlled food challenge (DBPCFC) [90,119,127]. Food challenge has been evaluated in adult and paediatric populations and found to correlate well with results of skin testing and RAST. Initially, it may be sufficient to perform two single-blind placebo-controlled challenges: if both are negative, no

Table 2. Laboratory tests

Confirmed relevance

- IgE antibody determinations
- Basophil degranulation tests
- Plasma histamine during provocation tests

Unconfirmed relevance

- Measurement of mast cell and basophil degranulation products
- IgA, IgM, and IgG antibody determinations
- IgG subclasses
- Food ags in serum
- Immune complexes in serum
- Tests for cell-mediated immunity (LIF, macrophage-activation, lymphocyte-proliferation, etc.)
- Complement analysis
- Serotonin
- Gastrointestinal permeability
- Somatostatin

allergy is evident. If one or both are positive, a DBPCFC should be performed [5]. This may be acceptable in children with atopic eczema and food allergy, but many would not wish (wisely so) to perform an oral challenge in a child with a definite past history of anaphylactic reactions to peanut. We must emphasize, that in our opinion, challenge or provocative trials with peanut are not to be considered if the patient's history suggests severe anaphylactic reactions [37,78,122].

Peanut oil allergenicity

Although it is generally assumed that refined (hot-pressed) peanut oil contains no proteins [128] and thus is not allergenic in peanut-sensitive patients [39,68,114,129–131], Moneret-Vautrin reported two cases of infants being allergic to infant formulae that contained peanut oil and linked the allergy directly to that ingredient [96,132]. Labial and oral provocation tests were positive with peanut oil in both children. Withdrawal and reintroduction of the formula confirmed its responsibility for the symptoms. Thus, even the small amount of peanut oil in the infant formula contained enough of the allergen to provoke symptoms. Four similar cases were reported by the same author in a recent paper [97]. These children suffered from atopic eczema and not peanut anaphylaxis. The importance of this finding must be viewed in the context that in 45 infant formulae, 11 contained peanut oil. To be 95% certain that 95% of peanut allergic individuals would not react to peanut oil in the formula, 58 individuals would have had to be challenged with no positive reactions (table of confidence limits for population failure rate), so some caution may still be necessary [79].

Using the 'dot-blot' technique, the other form of oil, cold-pressed (unrefined) oil has been shown to contain trace quantities of allergenic proteins [130,133]. It must be remembered that the so-called 'health foods' are frequently prepared with this type of oil.

Finally, peanut oil and other oils used to fry peanut-containing foods may be contaminated by released peanut allergens from the foods being cooked. They can therefore pose a potential and serious risk to peanut-sensitive individuals [39] as was demonstrated in the study of Keating *et al.* [68].

Treatment

The cornerstone of treatment of acute food allergy is avoidance of the offending food [134]. Other methods such as oral or cutaneous desensitization [135–137], prophylactic treatment with sodium cromoglycate [138–141], ketotifen [142], antihistamines [135] or

cyclo-oxygenase inhibitors [143] must be considered as of dubious long-term value or of no validated efficacy. New vaccines are becoming available which will bring hope to the peanut allergic patient.

Treatment of an anaphylactic reaction

This review is not the place to discuss the minutiae of treatment of such a life-threatening condition. What is of concern is to give the patient instruction and therefore security, that the treatment that they can administer to themselves may be sufficient in itself to abort an anaphylactic reaction or give them a 'window of time' so that they can reach an emergency department of a hospital for more specialized and intensive management.

Adrenaline (epinephrine) is the most important drug to be given in this condition. The pressure activated EpiPen syringe is one of the most convenient for patient use. Ideally it should be given intramuscularly into the outer aspect of the thigh as soon as the patient realizes the severity of their condition. If the reaction has already occurred, the patient should be placed in the recovery position, pulse and breathing checked regularly, and resuscitation started if necessary. A second injection can be given after 5 or 10 min as adrenaline is rapidly metabolized.

The aerosol of adrenaline (Medihaler Epi) has been recommended as an alternative to injection. Approximately 25 puffs of the aerosol is equivalent to 0.4 mg of adrenaline given subcutaneously. The aerosol can be puffed into the oral cavity where absorption is good. As with injection, this can be repeated after 5–10 min. The dose of adrenaline must obviously be adjusted for age and weight. The authors recommend that an injection is given in the first instance.

It cannot be stressed too strongly that early administration of adrenaline is paramount; it is always better to give one dose too many than not give an injection until too late. This is clearly shown in studies of fatal and near fatal reactions to food, including peanut. The most important factor that appeared to contribute to a fatal outcome following ingestion of peanut was the failure to administer adrenaline immediately following the onset of symptoms [20].

Other measures such as immediately washing the mouth out may be useful [11] and in very severe reactions gastric lavage has been tried in an effort to decrease further antigen absorption [13].

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