

THE DEVELOPMENT OF PEANUT ALLERGY AND THE ROLE OF ENVIRONMENTAL EXPOSURE

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BACKGROUND

The prevalence of peanut allergy (PA) in children has gradually increased over the years and is now believed to affect 1–2% of all children in Western countries.^{1–3} This is in conjunction with an overall increase in the prevalence of all food allergies in children in the past two decades.⁴ In addition, PA remains one of the leading causes of food-induced anaphylaxis⁵ and has also been shown to be the leading cause of death related to food allergy in a number of countries.^{6–10} However, it should be noted that death from food allergy still remains uncommon and is, in fact, relatively rare in children.¹¹ Yet the impact of having PA can be enormously burdensome, leading to increased anxiety, the limitation of social activities and an overall reduction in the quality of life for children and their families.^{12–13}

As with all food allergies, avoiding the allergen and treating allergic reactions appropriately continue to be the mainstay of managing PA. Work has been done on inducing peanut tolerance by oral immunotherapy (OIT), but its role is limited to increasing the threshold of reactivity to peanut and has not been shown to induce long-term sustained oral tolerance. Anagnostou et al (2014) demonstrated that peanut OIT raised the reactive threshold so that up to 91% of participants could tolerate a daily ingestion of approximately five peanuts.¹⁴ However, Vickery et al (2014) showed that only 50% of those who underwent five years of peanut OIT had sustained unresponsiveness (SU) one month after discontinuing OIT.¹⁵

This leads us to look at ways of preventing PA as this is likely to be the most effective way of reducing its incidence and prevalence. Prevention can be tackled only when there is a thorough understanding of the mechanisms underlying the development of PA. In recent years, a number of studies have brought to the forefront the importance of the role of environmental peanut exposure and the disrupted skin barrier in the development of PA.

THE NATURAL HISTORY OF PA

The median age at which PA presents is 14 months,¹⁶ and PA commonly persists into adulthood. Peters et al (2015) demonstrated that only 22% of patients who had a food-challenge of PA confirmed at one year of age had resolution of PA by four years of age, also confirmed by a food challenge.¹⁷ However, there is evidence that the incidence of resolution of PA may be greater if it were to include those patients who have never had a reaction to peanut but have been shown to be sensitised or have allergy as diagnosed by SPT or specific IgE only.¹⁸ It should also be noted that those patients who have experienced anaphylaxis in response to peanut are unlikely to have their allergy resolved.¹⁹ A number of studies have also

highlighted that peanut sensitisation (PS) and PA can recur following a negative food challenge if patients do not ingest peanut frequently or do so in significant amounts after that.^{18,20–21}

THE IMMUNOLOGICAL MECHANISM OF PA

The body's immune system can be exposed to allergens via a number of routes; these include the gastrointestinal tract, the respiratory tract and the skin. The pathophysiology of food allergy involves the initial exposure of the allergen (eg peanut) to the immune system. Once the allergen has been introduced into the body, antigen presenting cells (APC) engulf the allergen and interact with naive CD4+ T-helper lymphocytes. These T-helper cells then activate

B cells, triggering them to mature into plasma cells and produce antigen-specific antibodies (IgE) to peanut. The plasma cells continue to produce and secrete specific IgE to various peptides of peanut protein. The IgE bind to the surface receptors of mast cells in a number of sites around the body, including the GI tract, the respiratory tract and the skin. They also bind to basophils circulating in the peripheral blood. After the immune system has been primed (sensitisation), repeat exposure to the allergen leads to peanut peptide binding to specific IgE bound to mast cells and basophils causing these cells to degranulate and release a number of inflammatory mediators such as histamine, leukotrienes and cytokines, which leads to the signs and symptoms of an allergic reaction. Symptoms may involve the cutaneous organ systems (rash, hives and angioedema), respiratory tract (wheeze, stridor), gastrointestinal tract (vomiting, diarrhoea) and/or cardiovascular system (low blood pressure, pallor and collapse).

FACTORS ASSOCIATED WITH DEVELOPMENT OF PA

There are a number of factors that contribute to the development of PA. There are those factors relating to exposure and others relating to individual susceptibility, such as genetics and ethnicity.

GENETICS AND ETHNICITY

Twin studies have shown that there is a 64% concordance rate in the development of PA in monozygotic twins.²² Hourihane et al (1996) assessed 622 adults and children and their families with suspected PA in the United Kingdom (UK) and showed that grandparents reported PA in 0.1% of cases, aunts and uncles in 0.6%, parents in 1.6%, and siblings in 6.9%; therefore, only sibling history of PA increased the risk. Further evaluation by SPT and diagnostic OFC revealed a 7% prevalence of PA in siblings of peanut-allergic individuals.²³

A number of reports have also highlighted that children of non-white ethnicity are more susceptible to the development of PA.^{24–26} Fox et al (2015) found that the rate of increase in PA was greater in non-white children than white children;²⁶ they conducted an ethnicity-based study of children given a diagnosis of PA at a UK tertiary allergy clinic over a 14-year period between 1990 and 2004, with children with egg allergy as control subjects. Among the patients with PA there was a 23.5% increase (from 26.82% to 50.31%, $p = 0.001$) in the proportion of non-white subjects given a diagnosis of PA over time. As a comparison, among non-white children there was a <1% change in egg allergy over the same timespan.

EXPOSURE

A number of routes for peanut sensitisation have been proposed and there are varying amounts of evidence to support these.

a. *In-utero*

The available evidence thus far suggests that the in-utero development of sensitisation to peanut is unlikely. The Avon Longitudinal Study of Parents and Children (ALSPAC) was a birth cohort study comprising almost 14 000 pregnant women. Cord blood was assessed retrospectively from the mothers of children who developed challenge-positive PA. The group found no detectable peanut-specific IgE (level >0.35 kUA/L) in cord blood.²⁷ Another study demonstrated that any detectable peanut-specific IgE in cord blood is likely to be maternal in origin, because peanut-specific IgE was no longer detectable once the infant had reached six months of age.²⁸

b. *Breastmilk*

Vadas et al (2001) demonstrated that peanut protein, including major peanut allergen proteins Ara h1 and h2, can be detected in maternal breastmilk.²⁹ Their study looked at peanut protein levels in breastmilk in hourly intervals after mothers had consumed 50 g of dry-roasted peanuts and showed these were detectable within three hours of ingestion. Other studies have also reported detectable peanut protein in breastmilk in a proportion of women studied after maternal consumption of peanut.^{30–31} However, presence of peanut protein in breastmilk does not necessarily correlate with the development of PA via exposure to peanut protein in breastmilk. The ALSPAC study and another large UK cohort study, the Isle of Wight study, did not find any correlation between maternal peanut consumption during pregnancy and breastfeeding with PS or PA in children.^{27,32}

The CoFAR2 study, an observational study of infants at high risk of developing PA (due to eczema or egg and/or milk allergy), found that maternal peanut consumption during breastfeeding was not linked to the development of PA.³³ However, they did show that maternal peanut consumption during pregnancy in infants who were formula fed were more likely to have PS than those babies who were breastfed.³³ Among 71 infants who were formula fed only, the frequent maternal consumption of peanut during pregnancy was strongly associated with peanut IgE >5 kUA/L (OR 4.99, 95% CI, 1.69–14.74; $p < 0.004$). This suggested a protective effect of peanut consumption during breastfeeding. More recently, a Canadian study showed that it was the combination of peanut consumption during breastfeeding and introduction into the child's diet before 12 months that conferred the lowest rate of PS in the children at seven years of age, whereas either of these exposures in isolation increased the risk of PS.³⁴

c. *The environment*

The skin and the respiratory tract are two possible major routes for peanut sensitisation via exposure from peanut protein in the environment and there is a varying amount of evidence to support this, detailed below.

i. Airborne peanut protein

The evidence for PS occurring through the respiratory tract is weak as there is little evidence to support peanut protein being airborne.^{35,36} In the study by Perry et al (2004) participants wore air-sampling monitors and ate and stamped on peanuts in an enclosed room. The monitors did not detect any significant airborne peanut-protein allergens.³⁶ Brough et al (2013a) evaluated airborne peanut using sensitive polyclonal ELISA directed against peanut protein. They also used personalised air-sampling monitors in a number of situations – 1 cm above peanut butter and a dry-roasted peanuts packet, while eating peanuts and simmering satay sauce on a stove. They found that peanut protein was not detectable in these situations. Peanut protein was detectable during active peanut shelling but disappeared immediately after shelling was discontinued.³⁵

It should be noted that airborne peanut in planes with recirculated air may provide different findings. It has been reported that peanut protein has been detected in the ventilation system filters of commercial airliners after 5 000 flight hours using an inhibition assay with peanut extract; however, this abstract was never published.³⁷ In addition, a survey of peanut-allergic individuals reported allergic reactions to peanut on planes, presumed to be due to environmental exposure; however, this could have been from either peanut on surfaces rather than airborne peanut, given that peanut has been detected on aeroplane tray-tables (both when staff served peanut and when they did not, albeit at much lower levels).^{38,39}

ii. Peanut protein in environmental surfaces and dust

There is an increasing body of evidence suggesting sensitisation via the skin as a route for developing PA.^{40–43} In order for sensitisation to occur via the skin it follows that there must be peanut allergen in the environment. Fox et al (2009) carried out a study which used household peanut consumption as an indirect marker for environmental peanut exposure.⁴⁴ The group demonstrated that household peanut consumption during infancy was associated with an increased risk of PA in these children. They compared peanut-allergic children with atopic controls (non-peanut allergic but egg allergic) and non-atopic controls. They showed that household peanut consumption was significantly higher in peanut-allergic children (18.8 g/week) than in egg-allergic children without PA (1.9 g/week) and three times higher than in households with non-atopic children with no PA. There are several studies that have demonstrated the presence of peanut proteins in the environment at home,^{35,45} in schools and in preschools.^{46–47}

Brough et al (2013) demonstrated that household consumption of peanut correlated highly with peanut protein levels in dust from bedrooms, living rooms and kitchens.⁴⁵ They also found a positive correlation between household peanut consumption and peanut protein found

on surfaces such as the infant's bed, cot sides and play area, even when the infants did not consume peanut themselves. In addition, the group looked at potential routes of peanut protein transfer into the environment after the consumption of peanut.³⁵ They found that peanut protein was still present on hands and saliva for up to three hours after consumption. In addition, even after cleaning household surfaces with detergent, the surfaces were still found to contain detectable levels of peanut protein. Furthermore, peanut protein in dust has been shown to be biologically active, as basophils from peanut-allergic children were activated in a dose-dependent manner on exposure to dust extracts containing peanut protein.⁴⁵ The above studies support the hypothesis that household peanut consumption leads to increased exposure to peanut protein in the environment during infancy.

THE SKIN, PS AND PA

There is increasing evidence that a disrupted skin barrier is linked to the development of food sensitisation and food allergy. The disrupted skin barrier may take the form of clinical diagnosis of eczema, filaggrin loss-of-function mutation or demonstration of dry skin as measured by transepidermal water loss (TEWL).⁴⁰

a. Eczema

The association between a disrupted skin barrier, in the form of eczema, and the development of food sensitisation or allergy has been established in a number of studies, such as the Melbourne Atopy Cohort (MAC) study^{48–49} and the HealthNuts study.⁵⁰ In the MAC study, infants with a history of mild eczema had a three-fold increased risk of developing IgE food sensitisation compared with those with no history of eczema (36% vs 11%). Furthermore, infants with a history of severe eczema had a six-fold increased risk of developing food sensitisation compared with those infants without eczema (65% vs 11%). In the same cohort eczema before six months was associated with an increased risk of having a new food sensitisation as measured by SPT at one year (Hazard Ratio = 2.26, 95% CI = 1.34–3.82, 29.4% vs 13.8%).⁴⁹

The HealthNuts study, a large population-based cohort study of infants, found that infants with eczema were six times more likely to have egg allergy and 11 times more likely to have PA by 12 months than infants without eczema. The study also found that 50% of infants with early onset severe eczema (<3 months of age and requiring doctor-prescribed topical corticosteroid treatment) developed a challenge-proven food allergy.⁵⁰ Data from the ALSPAC study also demonstrated that infants who were exposed to topical peanut oil (in the form of Arachis oil) were at an increased risk of PA, but only if they also had eczema.²⁷ In addition, a history of eczema modified the impact of environmental peanut exposure on PS and PA in infants in the CoFAR2 study;⁴² in children with a history of eczema, each log2 increase in peanut-dust levels increased the odds of PA by 2.34 (95% CI; 1.31–4.18 $p < 0.01$).

b. *Filaggrin loss-of-function mutation*

Filaggrin (*FLG*) is a filament aggregation protein that plays an important role in maintaining the integrity of the skin. Mutations in the *FLG* gene lead to the abrogation of the normal flattening of keratinocytes in the stratum corneum and a reduction in natural moisturising factor (breakdown product of filaggrin).⁵¹ *FLG* loss-of-function mutations have been associated with eczema and skin barrier dysfunction, as demonstrated by raised TEWL. Brown et al (2011) demonstrated there was a positive association between children with *FLG* loss-of-function mutations and challenge-proven PA.⁵² An association with *FLG* loss of mutation and food allergy and food sensitisation has also been demonstrated in a number of other studies.^{53–54}

Brough et al (2014) demonstrated that children with *FLG* loss-of-function mutations not only had an increased risk of PS but also challenge-proven PA.⁴³ As part of the Manchester Asthma and Allergy Study (MAAS) it was shown that there was a dose-responsive relationship between early environmental peanut protein exposure in the home and PS and PA in children with *FLG* loss-of-function mutations. It was shown that for every natural log (*ln*) unit increase in peanut-protein exposure via house dust during infancy, these children had a five-fold increased odds of PS (OR 5.2 95% CI: 2.1–13.1, $p < 0.001$) and a three-fold increased odds of developing challenge-proven PA (OR 3.2 95% CI: 1.1–9.8, $p = 0.04$). Therefore the more concentrated the exposure to peanut levels in dust during early life the higher the risk of subsequent PS and PA.⁴³

c. *Skin-barrier impairment as measured by TEWL*

A study by Flohr et al (2014) found that a functional assessment of the integrity of the epidermis using TEWL was associated with food sensitisation even after adjusting for atopic eczema and *FLG* mutation status.⁵⁵ Kelleher et al (2015) measured TEWL at day 2 of life and again at two months and six months and they found that TEWL levels in the upper quartile preceded the onset of clinical eczema at one year of life.⁵⁶ Impairment of the skin barrier at day 2 of life was also predictive of food sensitisation and food allergy at two years of age.⁵⁷ Even in those without eczema, infants with upper-quartile TEWL levels on day 2 were 3.5 times more likely to have food allergy at two years than infants in the lowest quartile. To date, no study has assessed whether there is an interaction between peanut-dust exposure and high TEWL.

In summary, these studies support the outside-in hypothesis for the pathogenesis of eczema,⁵⁸ in that skin-barrier disruption occurs before the onset of Th2 inflammation. They also suggest that children with a disrupted skin barrier are at increased risk of PS and PA from environmental peanut exposure.

DUAL-ALLERGEN EXPOSURE HYPOTHESIS

The dual-allergen exposure hypothesis proposes that early

oral exposure to food protein induces tolerance, whereas early cutaneous exposure to environmental food allergen results in food sensitisation and allergy development. Randomised controlled trials such as the Learning Early About Peanut (LEAP) and Enquiring About Tolerance (EAT) studies both support the concept of inducing tolerance by early oral exposure.^{59–60} It is thought that the balance and timing of the two different routes of exposure, particularly in atopic individuals, determines this outcome and that early gut exposure to food allergen primes the immune system to develop tolerance, but that early exposure to food allergens via the skin leads to sensitisation and allergy.^{41,61} This hypothesis is supported by evidence in a study by Fox et al⁴⁴ that high levels of early oral exposure to peanut in infants abrogated the risk from high peanut consumption in households. To date the impact of oral peanut consumption on exposure to high peanut-dust levels has not yet been evaluated.

CONCLUSION

In summary, the collective data demonstrate that there is a reduced risk of PA if exposure to peanut protein is early and via the oral route. There is also evidence that environmental exposure, in the form of peanut protein found in dust, is associated with an increased risk of PS and/or PA in children with a disrupted skin barrier or the carriage of an *FLG* loss-of-function mutation, although causation has not been proven. The studies detailed above support the Dual Allergen Exposure hypothesis and could therefore provide a strategy for trying to prevent the onset of PA. Guidelines regarding the early peanut introduction for the prevention of PA in high-risk infants have been drafted in association with numerous international allergy societies.⁶² Studies to prevent the development of eczema through repairing the skin barrier are also showing promise,^{63–64} although these small studies did not show a reduction in food sensitisation. More recently, the PEBBLES (Prevention of Eczema by a Barrier Lipid Equilibrium Strategy) pilot study showed a trend in early emollient therapy to reduce the risk of food sensitisation.⁶⁵

DECLARATION OF CONFLICT OF INTEREST

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