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The Peanut Allergy Epidemic

Rivky Sachs

ABSTRACT

Peanut allergy is one of the most predominant food allergies. It accounts for majority of the highly severe and fatal allergic reactions to food. Peanut allergy is generally detected early in life and is commonly associated with other atopic disorders such as asthma, eczema, and rhinitis. The prevalence and pervasiveness of peanut allergies is increasing worldwide, and most peanut allergic patients have lifelong sensitivities to peanuts (de Leon et al, 2008).

Patients with severe allergies must stringently avoid any contact with peanuts and depend on intramuscular epinephrine (EpiPen) to counteract the reaction caused by intake of peanuts. Much research is dedicated to developing new treatments that may be able to induce tolerance in peanut allergic individuals without adverse side effects. This paper reviews the current understanding of clinical characteristics, pathogenesis, and hypothetical causes for the rise in prevalence of peanut allergies. It also discusses genetic risks and environmental effects of peanut allergy. Furthermore, it presents emergent future therapies and methods to prevent the development of peanut allergies in infants.

INTRODUCTION

Allergy is defined as an adverse immune response to food (Sicherer and Sampson, 2010). Such responses can be mediated by IgE antibodies aimed at specific allergens, or they can be triggered by other cellular activities (Wood, 2009). IgE mediated reactions are immediate, and symptoms can range from acute or chronic atopic reactions to fatal anaphylaxis. Non- IgE

mediated allergy occurs gradually and is evident by chronic skin conditions and gastrointestinal discomfort (Eigenmann, 2009). Peanut allergy is an IgE mediated response.

EXPOSURE TO THE FOOD ALLERGEN

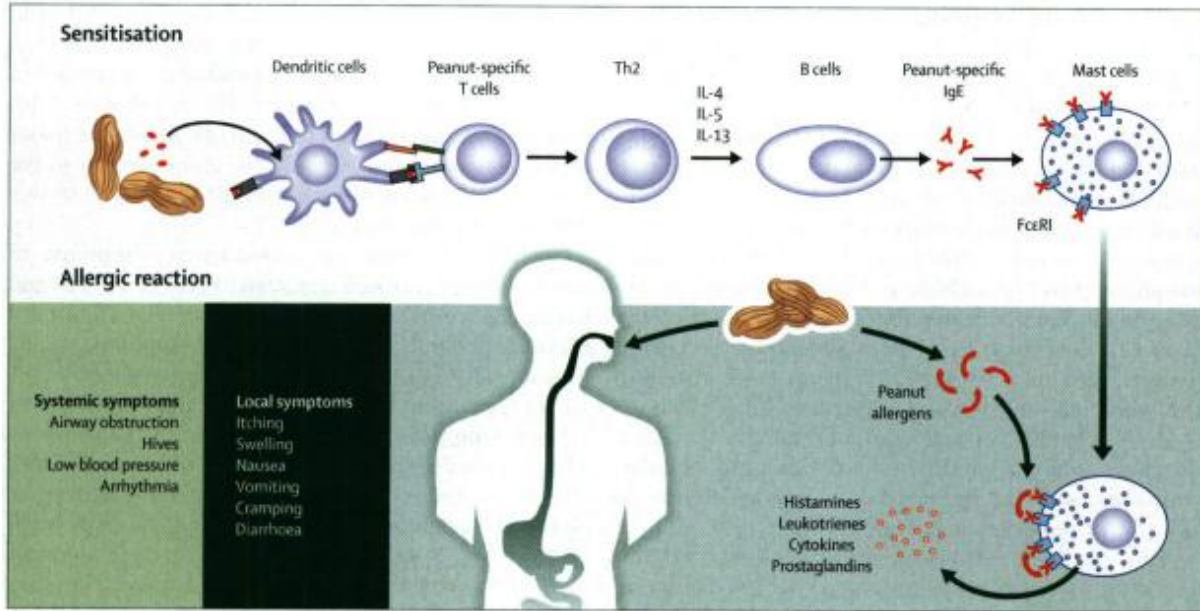
Peanut allergens are introduced to the body through one of three particular ways: ingestion, skin contact, or inhalation of airborne particles. In the most prevalent form of the allergy, peanuts must be consumed for an allergic reaction to ensue since the allergic reaction is not frequently activated by skin or air contact with the peanut allergen. Food enters the digestive system through the mouth and the food allergen is first introduced at the mucosal surface of the gastrointestinal tract (Burks, 2008).

PATHOGENESIS

At the mucosal surface of the gut, food proteins are digested by specialized epithelial cells that transfer them to antigen presenting cells such as dendritic cells which then process them into peptide fragments. These peptide fragments are presented on the cell surface by class II major histocompatibility complex (MHC) molecules. As the antigen presenting cell presents the antigen to T helper cells through MHC/T cell receptor interaction it activates the T helper cells. This process instigates humoral and cellular mediated responses that are associated with peanut allergy (de Leon et al, 2008).

In peanut allergic individuals, the activation of T helper 2 (T_H2) cells causes the production of cytokines such as interleukins including IL-4, IL-5, IL-9, and IL-13. These interleukins are released in increased amounts as compared to individuals that are not allergic to peanuts, thus exciting B cells to synthesize IgE antibodies. These peanut specific IgE antibodies are attached to mast cells in the gastrointestinal tract mucosa, skin, and respiratory tract mucosa and to basophils (Burks, 2003, Burks, 2008).

Upon ingestion of peanuts, the peanut proteins bind with the specific IgE antibodies on mast cells and basophils thereby secreting inflammatory mediators such as histamine. T_H2 cells and mast cells also produce tumour necrosis factor- α (TNF- α), IL-5, and chemokines, which cause eosinophils to accumulate at the site inflammation. Eosinophils stimulate the release of other inflammatory mediators which lead to clinical symptoms that will immediately develop (de Leon et al, 2008).



Allergic reaction to peanut (Burks, 2008)

CLINICAL SYMPTOMS

Clinical symptoms can be triggered by ingesting ten milligrams of peanut protein. The time it takes for symptoms to develop ranges from seconds up to two hours after ingestion. The majority of reactions of IgE mediated disorders include skin, respiratory, and gastrointestinal symptoms. Local symptoms include itching, swelling, nausea, vomiting, cramping, and diarrhea (Burks, 2008).

Anaphylaxis, a systemic symptom, can often be fatal. The early symptoms of anaphylaxis include oral and pharyngeal pruritus and chest tightness. Further symptoms of wheezing, hypotension, arrhythmia, and unconsciousness can develop into fatal and near fatal reactions (Lee et al, 2003). Anaphylaxis is a rapidly progressing multiple organ system reaction that can lead to cardiovascular failure. This reaction is a result of a massive release of mediators such as histamine (Sicherer and Sampson, 2010).

EPIDEMIOLOGY AND RISING PREVALENCE

Studies done in the United Kingdom and North America show peanut allergy prevalence rates in children have increased, in fact, almost doubling. Peanut allergy affects more than 1% of school aged children (Sicherer and Sampson, 2007). Grundy et al did two sequential cohorts in the Isle of Wight, United Kingdom six years apart. Children at the age of 3 and 4 received skin prick tests and those with positive results were given oral peanut challenges unless there was an otherwise convincing history of peanut allergy. The study confirmed an increase in peanut allergy from .5% to 1.0% between 1989 and 1995.

The same incidence was reported in the U.S. with rates similar to those received in the previous study. In 1997, Sicherer, Munoz-Furlong, and Sampson performed a population based, cross-sectional, random telephone survey in the United States using a standardized questionnaire. In 2003, they conducted a five year follow up study to compare the results of the prevalence

estimates. The study indicated a doubling in peanut allergy in children from 0.4% in 1997 to 0.8% in 2002.

Kagan and colleagues also confirmed the assumption of increasing prevalence of peanut allergy using diagnostic testing. They assigned questionnaires regarding peanut ingestion to parents of children in kindergarten through grade 3 in randomly selected schools in Montreal. Respondents were grouped as follows: (1) peanut tolerant, (2) never-rarely ingest peanut, (3) convincing history of peanut allergy, and (4) uncertain history of peanut allergy.

Groups 2, 3, and 4 received peanut skin prick tests (SPTs), and if responses in groups 2 and 4 were positive, measurement of peanut specific IgE was taken. Children in group 3 with a positive SPT were considered to have peanut allergy without more testing. Children in groups 2 and 4 who had peanut specific IgE levels less than 15kU/L were administered oral peanut challenges. These techniques ensured that only children who had real peanut allergic symptoms were considered sensitive. Their estimate of 1.5% proves that the prevalence of peanut allergy was even higher than what had previously been reported (Kagan et al, 2003).

However, five years later a follow up study was performed using the same methodology and population to determine whether prevalence was increasing over time. The prevalence estimate was 1.62%, indicating a .13% difference. They concluded that the prevalence has remained stable among this population. Furthermore, they refuted the studies conducted by Grundy et al and Sicherer et al by saying that the increasing prevalence estimates they reported was a result of environmental changes during the period that they experimented and that participation rates were lower at follow up, thus leading to an overestimate of prevalence. Also, they claim that the .4% difference in estimates of the case study done by Sicherer et al is not statistically significant (Ben Shoshan, et al 2003).

There are numerous problems with this follow up study done in Montreal and the conclusions drawn from its results. This study was conducted in one small region with low participation rates, as compared to the survey performed by Sicherer et al which covered the entire United States with a census of over 13,000 individuals. Therefore, .4% estimate is in actuality a large percentage of the population.

Moreover, they base their estimates on the assumption that peanut specific IgE levels of 15kU/L or greater indicate a peanut allergy. Consequently, they only presented peanut oral challenges to children who had positive SPTs with less than 15kU/L peanut specific IgE levels; even though there is no proof that a positive peanut specific IgE level implies that an individual does indeed have a peanut allergy. According to recent studies, between 50% and 75% of patients with specific IgE to food are not allergic to the food (Roberts et al 2005). On the contrary, in the study done by Grundy et al, all children with positive skin prick tests, not including those with a history of peanut allergy, underwent oral challenges regardless of their peanut specific IgE level. They did not rely on peanut specific IgE levels to determine if the child has a peanut allergy. Due to this and many other incorrect assumptions, this study loses its credibility. In addition, their criticism and disapproval of other studies is inherently biased and lacks evidence.

Over the past twenty years there has been a universal increase in children being diagnosed with this allergy (Grundy et al, 2002). The rise in prevalence of peanut allergies has

initiated much research in this field. There are numerous new hypotheses and theories to explain the apparent peanut epidemic.

SPECIFIC PEANUT ALLERGENS

Antigens that involve an IgE response are referred to as allergens, which are the glycoproteins found in food. Eight peanut allergens have been discovered and are classified as Ara h 1 to Ara h 8 (Burks 2008). The three major peanut allergens are Ara h 1, Ara h 2, and Ara h 3. Ara h 1 and Ara h 2 are known to be highly allergenic, because numerous peanut allergic individuals have serum specific IgE for these allergens.

The classification of Ara h 3 has not yet been identified: one study showed serum IgE reactivity in 44% of peanut allergic subjects while another found it in 95% of the patients. Ara h 4-7 are not as reactive with IgE in patient sera and have not yet been classified. Ara h 8 is different than the others as it is established to be a major allergen in Central Europe in individuals who display a co-allergy to peanut and birch pollen (de Leon et al, 2008).

BIOCHEMICAL PROPERTIES OF PEANUT ALLERGENS

According to Koppelman et al, many peanut allergens have specific physiochemical properties that display resistance to digestive enzymes and heat processing. Their study proves that Ara h1 is heat stable, although its structure is changed significantly when heated. The resistance of some peanut allergens to heat and enzymes may be connected to their ability of forming stable dimer and trimer complexes. This enables the peanut proteins to reach the intestinal mucosa intact, thus increasing their allergenicity and effectiveness.

MAILLARD REACTION

A major reaction that happens during the browning or processing of foods is the Maillard reaction. One of the main chemical modifications that peanut proteins undergo is the Maillard reaction which reduces sugars and primary amine groups thus increasing the allergic properties of peanuts. Maleki, Chung, Champagne, and Raufman proved this by conducting an in vitro model copying the Maillard reaction. Ara h 1 heated in the presence of sugars exhibited increased allergenicity, while Ara h 1 heated without sugars degraded and was barely discernible. Roasted peanut extracts were found to bind to IgE serum of allergic individuals at about 90- fold higher than raw peanuts. The Maillard reaction contributed to this effect. This study supports the findings of Nordlee et al that roasted peanuts bind IgE at higher levels than raw peanuts. It also shows that modification of proteins during the roasting process increases the IgE binding sites and enhances other allergenic properties in peanuts (Maleki et al, 2000).

EFFECTS OF COOKING METHODS ON PEANUT PROTIENS

There is a much lower prevalence of peanut allergy in China than in the United States, even though there is a higher rate of peanut consumption in China. Peanuts are fried and boiled in China; whereas they are usually roasted in the U.S. In 2001, Beyer et al conducted a study to examine whether the method of preparing peanuts could be a contributing factor to the difference of allergy prevalence between China and the United States. The Chinese-American population seems to have a similar prevalence of peanut allergy as the general U.S. population, so genes cannot account for this difference.

Two kinds of peanuts grown in the United States were roasted, boiled, and fried. Proteins were examined using SDS-PAGE and immunoblotting. Reactions to the peanuts were compared by using immunolabeling with sera from 8 individuals with peanut allergy. Frying and boiling modified the proteins of both types of peanuts in a similar way. The roasted peanuts had more Ara h1 which resulted in an increase in IgE binding intensity as compared to the boiled and fried peanuts. Furthermore, in the fried and boiled peanuts there was less IgE binding to Ara h 2 and Ara h 3 than there was in the roasted peanuts.

Beyer et al concluded that frying and boiling peanuts, as done in China, reduces the allergenic property of peanuts as compared to the roasting method which is widely used in the United States. Roasting uses higher temperatures that probably strengthen the allergenicity of peanut proteins by causing permanent changes in the structure and may account for the difference in prevalence of peanut allergy in the two countries (Beyer et al, 2001).

Although this study has strong supporting data, the tests performed are statistically insignificant and do not prove its hypothesis. There were only 8 samples of patient sera taken to compare the different reactions. This is a very small range with little diversity, and it does not differentiate between age groups. Recent statistics confirm that there are in fact more children with peanut allergies in China than what was initially thought (Burks, 2008). This does not invalidate the studies that show that roasting enhances peanut allergenicity. More information is needed about the prevalence of peanut allergy to better understand this subject matter.

ARA H 2 FUNCTIONS AS A TRYPSIN INHIBITOR

In their previous study, Maleki et al showed that the allergenicity of peanut proteins is enhanced due to thermal processing. Because of the increasing prevalence of peanut allergy and the severity of the symptoms, another study was performed by Maleki and his colleagues to find out whether any specific functions are associated with the major peanut allergen, Ara h 2, and whether these functions are affected by processing. Maleki et al conducted a protein domain homology search to figure out the functions of Ara h 2. Reputed functions were tested via enzyme assays and protein gel electrophoresis. Afterward, the structural properties of Ara h 2 from purified and roasted peanuts were compared.

According to their results, Ara h 2 purified from peanuts acts as a trypsin (digestive protein) inhibitor and roasting increases the trypsin inhibitory activity by a 3.6-fold. Ara h 2 was also found to protect Ara h 1, a second major allergen, from trypsin digestion. This characteristic was improved in Ara h 2 purified from roasted peanuts.

The data indicates that thermal processing may play a significant role in increased allergenicity of peanuts. Not only does roasting change the structure and stabilize peanut proteins as has already been proven, but it also alters its functional properties which further contribute to its increased allergenicity. Ara h 2 increases its resistance toward and provides Ara h 1 with extra protection against trypsin digestive enzymes (Maleki et al, 2003).

GENETIC RISK FACTORS OF PEANUT ALLERGY

It is implausible that genetic factors contributed to the increase of peanut allergy in certain parts of the world over the past decade. Nonetheless, it is probable there are genetic predisposing factors that contribute to the development of food allergy, just like there are genetic factors associated with other atopic diseases such as asthma and eczema. More research is

needed to figure out which genetic polymorphisms are associated with specific allergies (Lack, 2008).

Peanut allergy has been associated with familial inheritance and genetics. Hourihane, Dean, and Warner calculated rates of other atopic symptoms in people with peanut allergy and the prevalence of the allergy in their families. They concluded that a child with a peanut allergic sibling has a 7- fold increase of developing a peanut allergy (Hourihane et al, 1996).

A study was performed by Sicherer et al to determine if genetic factors influence peanut allergy by comparing the rate of this allergy among monozygotic and dizygotic twins. The method relies on the fact that monozygotic twins share all of the same genes, while dizygotic twins share only half of their genes. They found that there was a considerably higher peanut allergy association among monozygotic twin pairs than there was among dizygotic twin pairs. In monozygotic twins, a child has a 64.3% chance of developing peanut allergy if his/her twin has the allergy, while a dizygotic twin has only a 6.8% chance.

This data suggests that specific genes influence the development of peanut allergy in an individual. However, there are limitations to the results received in Sicherer et al's study. Firstly, it was impossible to get a population based sample, because of the low population rate of twins with peanut allergies. In addition, environmental factors affect gene expression and are also responsible for the increasing prevalence of peanut allergy.

VITAMIN D HYPOTHESES

The vitamin D hypotheses have been developed to explain the increase of allergies and asthma, and it involves two opposing studies. One is the vitamin D excess hypothesis which proposes that increased Vitamin D level results in a higher prevalence of allergies. The vitamin D deficiency hypothesis argues the opposite. Wjst, the first to work out the vitamin D excess hypothesis, recognized that in German farming communities there was less vitamin D supplementation in food and less allergies found in children. The theory was further advanced when they found an increase in allergies in Bavaria which happened around the same time that vitamin D supplementations were added to children's diets to prevent rickets. Milner et al and Hypponen et al both performed studies which proved that infants who had vitamin D added to their diets were at a greater risk for developing food allergies.

Those that support the vitamin D deficiency hypothesis say that people who do not get enough vitamin D from sunlight have a greater prevalence of allergies. They proved that countries further from the equator are less exposed to sunlight yet have higher rates of asthma (Lack, 2008). One intriguing study performed by Camargo et al provides evidence for the vitamin D deficiency hypothesis. They observed a strong north-south gradient for the prescription of EpiPens in the United States. In the New England region 8-12 EpiPens per 1000 persons were being distributed, while the southern states had only 3 EpiPen prescriptions per 1000 persons. Their data supports the presumable association between low vitamin D rates and allergies. There are proofs to substantiate both of these hypotheses, yet the vitamin D controversy remains unresolved.

ORAL AND NONORAL EXPOSURE TO PEANUT ALLERGEN

Infants can be exposed to peanuts through ingestion or via environmental exposure such as topical use of peanut derivatives. Other types of exposure can occur in utero or through breast

milk (de Leon et al, 2007). The exposure route through which sensitization occurs remains unknown, and there are various schools of thought on this subject (Fox et al, 2009).

PEANUT AVOIDANCE DURING PREGNANCY, LACTATION, AND INFANCY

In order to reduce the prevalence of peanut allergy, the UK health department advised pregnant or nursing mothers to avoid eating peanut products if they themselves or other immediate family members of the fetus are atopic (Ewan, 1998). Hourihane et al conducted a study five years after the UK peanut avoidance advice which showed that the prevalence of peanut allergy in the UK increased. The authors concluded that the government's advice showed no significant influence on the outcome (Hourihane et al, 2007).

Similarly, the American Academy of Pediatrics committee recommended avoiding peanuts in the infant's diet during the first three years of life in order to prevent peanut allergy development (Baker et al, 2000). It was later confirmed that peanut allergy in children doubled since the recommendation was put into effect (Burks, 2009). However, it still remains tentative whether peanut avoidance during pregnancy and lactation has a positive, negative or no impact at all on the prevalence of this allergy in children (Hourihane et al, 2007).

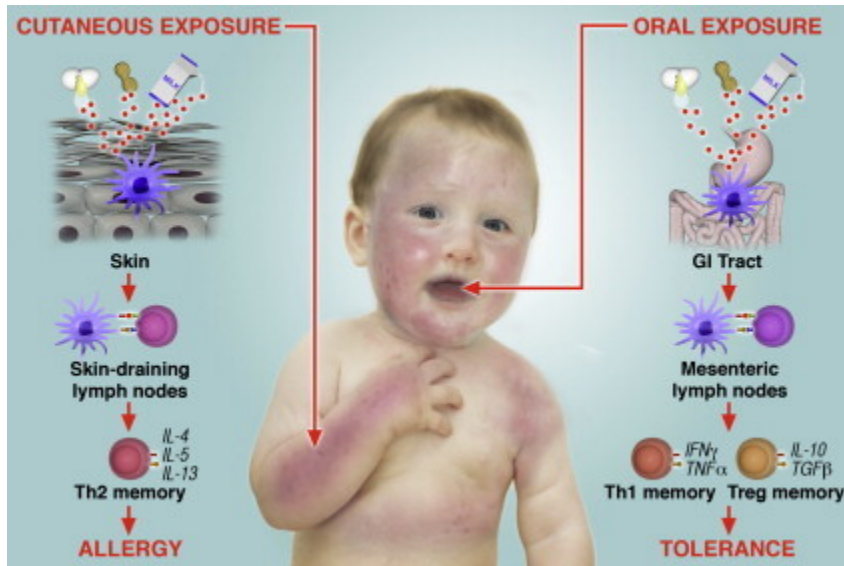
DUAL-ALLERGEN EXPOSURE HYPOTHESIS

Fox et al presented data substantiating a different theory in which low-dose early environmental exposure increases the probability of developing a peanut allergy as opposed to maternal consumption of peanuts. Since most children with peanut allergy react on their first oral exposure to peanut, they hypothesized that cutaneous exposure is the route through which allergic sensitization occurs. In a previous study, they showed that topical exposure to creams containing peanut oil was a risk factor for the development of peanut allergy. Almost 91% of the children with peanut allergy were exposed via use of peanut oil in the first six months of life. Moreover, in households where peanut is consumed a lot, there are other forms of environmental exposure that can occur such as cutaneous contact or inhalation of the allergen. For example, there is always remaining peanut allergen on the hands or in the saliva of someone who consumed peanuts. When an individual ingests peanuts and touches or kisses someone not yet exposed, it can cause sensitization.

At first, it seems that the results of the study demonstrate a strong association between increased maternal consumption of peanuts during pregnancy and lactation and children who develop peanut allergy. This inconsistency was resolved by adjusting for household peanut using logistic regression. They concluded that maternal consumption is irrelevant, since mothers in households with high peanut consumption are more probable to eat peanut because of its accessibility.

One group of children had high levels of environmental exposure and consumption of peanuts during infancy, yet they were tolerant to peanuts. This data supports the hypothesis that infant oral exposure to peanuts can induce tolerance and prevent development of peanut allergy even where there is environmental exposure as well. This study demonstrates that high levels of environmental exposure due to household consumption increases cutaneous sensitization to peanuts. It also refutes the original hypothesis that peanut consumption during pregnancy and lactation causes the development of peanut allergy in infants (Fox et al, 2009).

This theory is known as the dual-allergen exposure hypothesis. Low-dose early environmental exposure of peanut is taken up by Langerhan’s cells in the skin which leads to T_{H2} responses and release of IgE by B cells resulting in allergic sensitization. On the contrary, early infant consumption causes T_{H1} and regulatory T cell responses thereby inducing tolerance. This hypothesis reveals the connection between the presence of infant eczema and the ensuing development of food allergy. It also explains the rates of food allergies in different parts of the world and changes over time (Lack, 2008).



(Lack, 2008)

EARLY CONSUMPTION OF PEANUT

In order to investigate the effect of early consumption of peanut, Du Toit et al, compared peanut allergy prevalence among Jewish children in the UK and Israel. Israeli children consume peanut in high quantities early in life, while UK Jewish children avoid it altogether. Nonetheless, Jewish children in the UK had a peanut allergy prevalence of more than 10-fold higher than in Israel. Their findings imply that early and frequent high dose peanut consumption may thwart the development of peanut allergy (Du Toit et al, 2008). Furthermore, studies suggest that people in African and Asian countries, where the peanut allergy rate is relatively low, consume peanuts throughout pregnancy and infancy. Conversely, in the U.S., U.K., Australia and Canada peanut consumption is higher, yet there is a much greater prevalence of peanut allergy. This is due to the fact that there is a lot of environmental exposure accompanied by avoidance of peanuts during infancy (Lack, 2008).

Food allergies among allergy clinic patients

| Country | Peanut allergy (%) | Dietary practice recommendations (infant peanut consumption) |
|---------|--------------------|--|
|---------|--------------------|--|

| Country | Peanut allergy (%) | Dietary practice recommendations (infant peanut consumption) |
|--------------------------|--------------------|--|
| United Kingdom (n = 191) | 25 | Avoidance |
| United States (n = 300) | 69 | Avoidance |
| Israel (n = 992) | 2.1 | High infant consumption |
| Philippines (n = 184) | 0 | High infant consumption |

(Lack, 2008)

The results from these studies suggest a possibility that high levels of environmental exposure without oral exposure can result in peanut allergy, while elevated peanut ingestion can induce peanut tolerance. Further study is needed to investigate the validity of this hypothesis. It is extremely difficult to differentiate between the precise effects of maternal consumption and household peanut exposure. Moreover, there are other factors that can explain the difference in peanut allergy prevalence between Israel and England.

First, there may be a delayed increase in Israel since the prevalence of 0.17% that Du Toit et al recorded is a 4- fold increase from what was originally recorded by Dalal et al in 2002. Additionally, most peanuts in Israel are boiled which decreases its allergic properties as compared to being roasted which increases its allergenicity. Nonetheless, this promising theory is being investigated further by the Learning Early About Peanut Allergy study through a randomized controlled trial to assess whether early peanut consumption in high risk infants will prevent peanut allergy more effectively than avoidance during infancy (Burks, 2009).

FUTURE THERAPIES

Most of the clinical studies being performed on peanut allergy are devoted to finding an effective treatment to help patients with severe reactions to peanuts (de Leon et al, 2007). The standard subcutaneous immunotherapy has been eliminated because it resulted in many adverse reactions. Immunotherapeutic approaches to food allergy in general, have recently been categorized as food allergen-specific and food allergen-nonspecific. Presently, there is no cure for food allergy. The only treatment for peanut allergy is stringent avoidance of all peanut containing products. The immunotherapeutic approaches discussed below are tentative and require further research (Sicherer and Sampson, 2007).

SUBLINGUAL AND ORAL IMMUNOTHERAPY

Sublingual immunotherapy (SLIT) and oral immunotherapy (OIT) are both allergen specific therapeutic approaches. Both these therapies are designed based on the theory of induced tolerance when an antigen is presented at the oral mucosa/ gut associated lymphoid system. In SLIT and OIT, patients are introduced to small amounts of the allergen orally and the amount is increased over time. Although these therapies do provide desensitization for many patients on therapy, there is no proof that induces tolerance. Furthermore, there are risks of extreme side

effects and anaphylaxis if the patient stops therapy for 1-3 weeks and then resumes with the same dosage (Sicherer and Sampso, 2007).

MODIFIED PROTEIN VACCINE

The engineered recombinant protein strategy is an allergen-specific method which attempts to minimize IgE activation by mutating IgE binding sites. The three major peanut allergens are separated to identify their allergenic epitopes/ IgE binding sites (Nowak-Wegrzyn et al, 2009). Then, mutations are made to the peanut allergen gene which makes these sites nonreactive to IgE. When the mutated peanut allergen is expressed, it will result in hypoallergenic variants which can be used for immunotherapy (de Leon et al, 2007). This method is much safer than standard subcutaneous which injected the native protein into the skin. This approach looks very promising in murine models and human studies are being planned for further testing (Sicherer et al, 2010).

CHINESE HERBAL MEDICINE

Li and colleagues developed a 9-herb preparation known as Food Allergy Herbal Formula (FAHF-2), which is an allergen-nonspecific approach that prevents peanut induced-anaphylaxis (Sicherer and Sampson, 2007). In one experiment, peanut allergic mice treated with FAHF-2 for 7 weeks were challenged 1, 3, or 5 weeks after therapy. They recorded that IgE levels were particularly reduced by FAHF-2 and remained that way as long as 5 weeks after therapy was completed. This result seems to be connected to the suppression of T_H2 cytokines by the FAHF-2. The full protection that FAHF-2 demonstrated was replicated in many experiments and always showed a consistent response. This herbal formula might prove to be a valuable and harmless treatment for peanut allergy (Srivastava et al, 2005)

ADDITIONAL IMMUNOTHERAPEUTIC METHODS

Other types of food allergen-specific therapies include cytokine-modulated immunotherapy, immunostimulatory sequence-conjugated protein-modulated immunotherapy, plasmid DNA-based immunotherapy, and allergen peptide immunotherapy. All these treatments try to lessen the T_H2 response or induce tolerance to a specific food allergen (Burks, 2008). One study shows that similar proteins found in soybeans can be used for immunotherapy to desensitize peanut allergic mice (Pons et al, 2004). Another allergen non-specific approach is anti IgE therapy which does not cure the allergy but rather reduces fatal reactions in patients (Burks, 2008). The responses to this therapy turned out to be inconsistent, and this method has been suspended due to safety issues (Nowak-Wegrzyn et al, 2009).

Selected immunotherapeutic strategies:

| Therapy | Immune rationale | Benefits | Observations to date |
|--|---|---|--|
| Standard subcutaneous immunotherapy (native allergens) | Antigen presentation in nonmucosal site results in T _H 1 skewing | Proved for venom and respiratory allergy, possible benefit (pollen) for oral allergy syndrome | Primarily avoided for risk of anaphylaxis (eg, peanut) |
| Sublingual/OIT | Antigen presentation to mucosal site provides desensitization and | Natural foods, reduced risk of systemic anaphylaxis compared with injections | Mounting evidence for desensitization and relative safety; unclear effect on |

| Therapy | Immune rationale | Benefits | Observations to date |
|---|--|---|---|
| | might induce tolerance | | tolerance |
| Modified protein vaccine | Reduced IgE activation by mutation of IgE-binding epitopes | A safer form of immunotherapy compared with injection of native protein | Murine models show promise, human studies are planned |
| Peptide vaccine (overlapping peptides) | Peptides are less likely to cross-link IgE, avoiding mast cell activation | No requirement for IgE epitope mapping/mutation | Limited |
| Conjugation of immune stimulatory sequences to allergen and additional adjuvant methods | Enhance T _H 2 response by activating innate immune receptors (using specific sequences or whole bacteria) | Increased efficacy, possibly improved safety | Preclinical studies |
| Plasmid DNA-encoded vaccines | Endogenous production of allergen might result in tolerance | Possible 1-dose treatment | Murine models reveal strain-specific response |
| Anti-IgE antibodies | Targeted toward Fc portion of antibody, can inactivate IgE with reduced risk for activating mast cells | Not food specific Some response in eosinophilic gastroenteropathy (pilot study) | Preliminary study showed improved threshold overall but did not show uniform protection |
| Chinese herbal medicine | Mechanism unknown | Not food specific | Murine models show efficacy Human safety studies are underway |
| Cytokine/anti-cytokine (eg, anti-IL-5) | To interrupt inflammatory signals | Might allow directed interruption of inflammatory processes without need for food restriction | Preliminary study shows benefit for eosinophilic esophagitis. |

(Sicherer et al, 2010)

CONCLUSION

It has been proven that peanut allergy is becoming increasingly prevalent and poses a health threat worldwide, specifically in developed countries. In peanut allergic individuals, the exposure of peanut allergens via the gut, skin, or air can lead to clinical symptoms ranging from mild skin conditions to fatal anaphylaxis. Much research has been done to investigate the immunologic, environmental, and genetic affects on the development of peanut allergy. Studies

show that peanut proteins undergo the Maillard reaction during thermal processing, thus increasing the allergenicity of peanuts. Furthermore, roasting uses elevated temperatures that strengthen the allergic properties of peanut proteins by causing permanent changes in its structure. Another study suggests that Ara h 2 purified from peanuts acts as a trypsin inhibitor and roasting increases the trypsin inhibitory activity.

Some studies propose that genetic factors are linked to the development of peanut allergy, while the vitamin D hypotheses suggest that either increased or decreased levels of vitamin D leads to increasing allergy prevalence. Furthermore, it was originally thought that avoidance of peanuts during pregnancy and lactation can prevent development of peanut allergy in the fetus/infant. However, this was disproven, and the dual allergen exposure hypothesis, which states that low-dose early environmental exposure increases the probability of developing a peanut allergy, is the newest proposition. There are some allergen specific and allergen nonspecific therapies available to reduce fatal peanut allergic reactions. Research is being done to provide a therapy that induces tolerance to peanut without adverse side effects.

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