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Possible Role of Environmental Factors in the Development of Food Allergies

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Abstract

The development of food allergies is thought to involve multiple factors, and it is unclear which conveys the most risk regarding this process. Since food allergy is a chronic disease without a cure at this time, understanding its development could provide an avenue for preventive practices and development of a curative treatment. Both historical and current data implicate maternal factors, genetics, and environmental exposures as major risk factors in the development of food allergy. An immature gut of the infant has been hypothesized as a possible route of sensitization. Breastfeeding until at least 6 months of age has been shown to have protective factors for the newborn and may possibly improve gut permeability. Newer studies such as the LEAP and EAT investigations also looked at early exposure and prevention of food allergies; their long-term results are critical in understanding early introduction and tolerance. Cutaneous exposure, oral exposure, and food protein exposure in house dust with their relation to the food allergy course are also a path of interest. Current research has shown sensitization can occur through impaired skin such as those with eczema and a filaggrin mutation. Tropomyosin and alpha-gal also are related to the complicated immunomodulatory factors involved in food allergy and allergic response. Cross-reactivity with plant allergens, sensitization to house dust mite and cockroach, and lone star tick bites can also induce food allergens in children and adults. Together, these factors provide a cohesive beginning to understanding how food allergies can occur and can influence further investigation into prevention, treatment, and eventual cure of food allergies.

Keywords Food allergy · Breastfeeding · House dust · Environmental exposure · Oral allergy syndrome · Tropomyosin

Introduction

Food allergy is a chronic disease that can affect a patient not only medically, but from a financial and social perspective. It affects 6–8% of young children with rates increasing over the past 10–20 years [1]. These allergies can be severe, and treatment is limited to avoidance and emergency management of reactions. Without a cure, there remains a significant risk and burden to both adults and children with food allergy. While the options of desensitization through oral immunotherapy (OIT) and epicutaneous immunotherapy (EPIT) are on the horizon as a treatment, these are not curative treatment. The eventual cure to food allergies will be understanding the cause behind their development, which is nuanced, as there are thought to be complex factors involving genetics, immunity, and environmental risks [1]. Other risks are atopic history in the patient, timing, and route of exposure to foods, and increased hygiene practices. The reduction in infection and creation of a "clean environment" has led our immune systems to work against natural products such as foods and plants in our environment. The risk factors and understanding development of food allergy continue to be an area of study, especially regarding the potential effects of inheritance. There is also a question of early food introduction leading to failure to acquire tolerance, which continues to be investigated [2]. However, the groundbreaking LEAP (Learning Early About Peanut allergy) study has completely transformed previous beliefs about early introduction of allergenic foods. Major factors thought to be involved in food allergy include

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breastfeeding, maternal diet, family history of food allergy, and environmental exposures.

Breastfeeding

Breastfeeding an atopic infant is a key intervention suggested to reduce the risk of atopic disease such as asthma and food allergy. Risk of atopic disease in infants with a biparental or parent and sibling with a history of atopy is 40–60%, and therefore, identifying preventative methods is key [1]. Evidence historically supports the beneficial impact of breastfeeding on eczema [3]. In addition, breast milk provides a protective effect on the newborn from infections, and there has been some data to note a reduction in adult risk of obesity and diabetes. Its effect on allergic disease, however, is debatable, and there has been no true benefit established. Early-life environment and diet are thought to have a link with later allergic disease development; immune response towards these exposures moderates the physiologic response manifested as an allergy. The different factors in breast milk confer passive immunity as well as impact the metabolism. The composition of breast milk depends on the mother and her diet. Immunomodulatory components of breast milk include cytokines, fatty acids, immunoglobulins, and leukocytes; although these vary, they can influence the outcome of food allergy in breastfed infants [4]. Food allergies target the gut mucosa, and when barrier dysfunction is present, a disease such as a food allergy can occur. At birth, the gut mucosa is immature and many factors that assist with barrier formation are deficient. Increased inflammation early in life due to individual stimuli may contribute to allergic sensitization to dietary antigens. Breast milk contains gut trophic factors and decreases the permeability of the intestinal epithelium to protein [5]. Absence of breastfeeding or decreased trophic factors in breast milk can lead to a higher rate of inflammation which prevents tolerance to dietary antigens and in fact promotes an allergic response.

A neonate's gut barrier homeostasis depends on maternal milk factors and the neonate's immunity, which is immature in early life. The gut barrier, which involves intestinal mucosa as a physical and immunologic gateway to the body, has an active role in preventing pathogenic proliferation. Microbiota in the gut consists of microorganisms which includes these pathogens as well as harmless and necessary gut bacteria. Due to the presence of pathogenic gut bacteria, the neonate's immune system development is key in preventing disease [6].

An immune response involving T helper type 2 (Th2) cells is generally implicated in allergic reactions, and there is a complex interplay of immunity and breached gut barriers in food allergy. Breast milk and maternal IgA present in breast milk help to diversify gut bacteria and decrease the risk of gut barrier breach [5]. Breast milk contributes to the neonatal gut protection due to transfer of IgA. The IgA in breast milk is resistant to digestion and protects neonates from gut pathogens due to antigen binding. This is especially critical due to neonatal immature immune systems. The newborn gut is vulnerable and hypersensitive to inflammatory stimulation, and breast milk can also suppress this proinflammatory reaction due to immunomodulatory molecule production [6]. Metabolites are produced and transferred to the infant through breast milk and are thought to encourage immune system maturation and antimicrobial peptide synthesis in the neonatal gut. It was hypothesized by Munblit et al. that probiotics given to pregnant mothers would modulate their gut microbiota and subsequently affect their children, but studies were inconclusive [5]. Probiotics increased the levels of immunomodulatory factors in breast milk in some studies, but the overall impact on allergic disease in the neonate with maternal probiotic administration is unknown. It was noted that in mother supplemented with the probiotic bifidobacteria, some infants had increased numbers of bifidobacteria in the infant gut. However, this was not consistent in all patients [5]. It is not thought that probiotic administration to the mother produces a significant result in the neonate regarding prevention of food allergy, but further study is needed.

Current recommendations from the World Health Organization and American Academy of Pediatrics are for exclusive breastfeeding for at least 6 months, and research showed early food introduction of potentially allergenic foods could decrease the risk of food allergy development. Therefore, food protein transfer via breast milk would be an important method of initial exposure of food [5]. Food consumption and appearance of those food proteins in the breast milk have limited data and it is unclear how much protein is transferred. There is a lack of direct correlation between how much maternal protein is consumed and how much is noted in breast milk. For example, Munblit et al. note that peanut exposure in utero results in production of maternal antibodies in serum and breast milk which are transferred to the fetus [5]. There are also variations in duration of breastfeeding which can affect studies looking at the protective effect of breast milk regarding food allergy prevention.

There is conflicting data regarding the effect of breastfeeding on allergic disease development in the child. An unexpected finding in more recent studies is that breast milk has been identified as a potential risk for allergic disease development, especially a study from Japan showing potential increased prevalence of atopic dermatitis in breastfed infants. However, reverse causation should be considered in that infants at the highest potential risk for allergic disease due to family history or presence of early signs of allergic disease in the form of viral-induced wheezing and infantile eczema might be breastfed for longer periods of time due to recommendations that this may help with potential allergic disease [7]. Early signs of allergic disease are associated with reduction in risk of ceasing

exclusive breastfeeding; therefore, this could be a confounding factor in studies about breastfeeding and allergic disease.

Reverse causation-associated factors need to be considered such as family history and time of onset of allergic symptoms in the infants. When applied to school age children in Japan, data showed that those who were breastfed exclusively as infants had a higher risk of allergic disease based on the previously mentioned factors. Therefore, the risks were declared as confounding factors, and when analyzed as such, the promoting effect of breastfeeding on allergic disease disappeared. It was specifically noted that breastfeeding had an inhibitory effect on asthma prevalence at school age [7]. Based on these findings, it is unlikely breastfeeding has a promoting or preventive effect on food allergy, but further study is needed as has been shown by multiple studies showing inconclusive or contradictory data. Overall, the characteristics of breast milk from its composition to its known effects on the gut mucosa make it an ideal candidate to prevent allergic disease, but studies have shown no definite link towards this goal at this time [5].

Maternal Diet and Food Allergy

Studies have previously been completed using elimination diets in expectant mothers with at least one atopic family member. One such study involved elimination of cow's milk and egg from 28-week gestation to delivery, and they found proportions of atopy in the children were equal in childhood [8]. Food intolerance to egg, however, was noted to be more common, but there was no overall long-term difference noted. Peanut allergy has a long and severe history compared to other food allergies, and in utero sensitization to this dietary allergen may play a role in the disease. Mothers who consumed peanuts more than once a week during pregnancy had a higher likelihood of a peanut-sensitized child, although there was no identified relationship between peanut consumption during breastfeeding and sensitization in the child [9].

It is debatable whether maternal avoidance of allergenic foods can prevent food allergy development in infants, and recommendations are against elimination diets at this time [10]. It has been postulated that increasing ingestion of peanuts by pregnant or breastfeeding mothers may have a role in increased prevalence of peanut allergy, but confounding factors are varied and extensive [11].

Historically, studies have previously been performed using maternal elimination diets. The effect of avoidance during breastfeeding on peanut allergy prevalence is modest, as seen with other elimination diets, and there are no convincing long-term effects on food allergy overall [4]. Peanut exposure has been studied extensively, but there is no significant impact on development of peanut allergy with maternal peanut exposure during pregnancy and lactation despite the known transfer of maternal antibodies in serum and breast milk [12]. A study specifically evaluating wheat allergy and the effect of breastfeeding without dietary elimination as well as timed introduction of gluten also did not show a significant difference in risk of wheat allergy development [13]. Although there may be some evidence for cow's milk avoidance during breastfeeding reducing the risk of cow's milk allergy in infants, this is still a debated area of research [14]. In a Swedish study, breastfeeding mothers eliminated egg, milk, and fish for the first 3 months of breastfeeding versus a control group with no dietary restriction [15]. These products were reintroduced after 6 months, and by 10 years of age, there was no significant difference in atopic diseases of the children in either group [16]. Sensitization rates of both groups were also not significantly different; peanut sensitization was greater by skin prick test but not blood test and soy was greater by blood test and not skin prick test in the control group [17]. An equal number of patients in both groups had experienced food reactions. A study in the UK intervened in the aspect of infant feeding, using infants at high risk of atopy divided into a control and treatment group; the treatment group was fed a soy protein hydrolysate formula or breastfed by mothers undergoing an elimination diet excluding milk, egg, wheat, soy, orange, fish, and nuts. The control group was fed without precaution and with formula or breast milk [18]. After 9 months of age, these previously avoided foods were reintroduced, and at 4 years of age, the children in the control group without any dietary intervention had more definite rates of allergic diseases [19]. Food intolerance and sensitization via skin prick testing were higher in the control group. Confounding factors identified were environmental or dietary intervention over the years, and adding this into the interpretation resulted in a modest influence of maternal and infant diets on food allergy. Other studies with similar elimination diets showed no difference between control and elimination groups regarding food allergy or sensitization.

The Cochrane database states "prescription of an antigen avoidance diet to a high-risk woman during pregnancy is unlikely to reduce substantially her child's risk of atopic diseases, and such a diet may adversely affect maternal or fetal nutrition, or both. Prescription of an antigen avoidance diet to a high-risk woman during lactation may reduce her child's risk of developing atopic eczema, but better trials are needed. Dietary antigen avoidance by lactating mothers of infants with atopic eczema may reduce the severity of the eczema, but larger trials are needed" [10]. Studies have previously shown both benefits and risks of elimination diets, but in reviewing the evidence collected by all the prior studies and the Cochrane database, there is no significant evidence indicating that maternal elimination diets help prevent food allergy development in breastfed infants (Table 1).

Table 1 Early interventions to prevent development of food allergies

Intervention	Benefit
Breastfeeding	BM contains gut trophic factors and decrease permeability of intestinal epithelium
	Transfer of maternal IgA helps with gut immunity
	Immune system maturation
Early food introduction	LEAP study identified low incidence of peanut allergy in high-risk infants that were regularly fed peanut products before 1 year of age [20]
	EATS study did not show the efficacy of early introduction of allergenic foods in an intention-to-treat analysis. However, the consumption of 2 g per week of peanut or egg-white protein was associated with a significantly lower prevalence of these respective allergies than was less consumption [2]

LEAP and EAT

Regarding food allergy prevention, the "Learning Early About Peanut" (LEAP) and "Enquiring about Tolerance" (EAT) studies were groundbreaking in the field. Although they did not address maternal factors, the early introduction aspect and age-related analysis of food allergy development fall in line with prior studies referenced when looking at the significance of exposure and elimination. The LEAP study evaluated children between 4 and 11 months of age at high risk for peanut allergy and randomized them to groups of either complete peanut dietary elimination or peanut snack consumption at least three times a week. This study noted that 17% of children who avoided peanut developed peanut allergy by 5 years of age, and only 3% of children who ate peanut developed food allergy by the same age. Their conclusion was, therefore, that for high-risk infants defined as having severe eczema, egg allergy, or both, regular ingestion of peanut in the first 11 months is effective in prevention of allergy development [21]. The EAT study assessed if early introduction of commonly allergenic foods at 3 months of age in healthy breastfed infants without risk factors would prevent food allergies. The foods used were peanut, cooked egg, cow's milk, sesame, whitefish, and wheat. The results of the study did not show efficacy of early introduction in preventing development of food allergy; however, it did raise a question of whether prevention is dose-dependent [2]. There continues to be emerging research regarding elimination, early exposure, and dose dependence in prevention of food allergy in general, but peanut allergy has had a particular focus in the investigation (Table 2).

Family History of Food Allergy

Family history and genetic predisposition are theorized to be a risk factor for food allergy, but the contribution of genetic factors and the effect of the potential contribution is largely unknown. Another inherited risk is atopy in the patient, with comorbidities identifying some patients at increased risk for food allergy. Having food allergy may be related to risk of asthma, and vice versa [1]. Other inherited risks are family history related. A family-based study in Chicago in 2009 showed strong familial aggregation of food allergy and sensitization to food allergens especially among siblings [23]. However, more recently, it has been noted that sensitization without reactivity is common among siblings, but true clinical reactivity was not significant and did not justify testing siblings of children with food allergy [24]. There is some interplay between environmental and genetic factors affecting food-specific IgE, but absolute risk of food allergy development in siblings of children with food allergy is unclear [24].

Genetic studies indicate food allergies are polygenic, with hundreds of genes implicated. Heritability ranges from 15 to 30% estimated for food-specific IgE and 80% for peanut allergy. However, environmental exposure is still postulated to have a major role in the rise of prevalence of food allergy, as genetic association confers only a moderate level of predisposition [25]. Whether exposure has a beneficial or detrimental impact depends on multiple factors. The beneficial impacts of

Table 2 Addendum guidelines for evaluation and early peanut introduction [22]

Infant criteria	Recommendation	Earliest age of peanut introduction
Severe eczema, egg allergy, or both	Strongly consider evaluation with peanut-specific IgE and/or skin prick test and, if necessary, an oral food challenge. Based on test results, introduce peanut-containing foods	4–6 months
Mild to moderate eczema	Introduce peanut-containing foods	Around 6 months
No eczema or any food allergy	Introduce peanut-containing foods	Age appropriate and in accordance with family preferences and cultural practices

environmental exposure have been much debated recently as the hygiene hypothesis has been developed.

Cutaneous Exposures and Oral Exposures

The popularity of the hygiene hypothesis typically harkens back to a 2002 article in science in which the authors suggested that the increase of allergic diseases in the industrialized world could frequently be explained by a decline in infections during childhood [26]. The corollary that these authors proposed was that the induction of a robust anti-inflammatory regulatory network is aided by persistent immune challenge resulting in an inverse association between numerous infections and allergic disorders. In other words, the immune system is much like muscle. The more you exercise it the better it gets. Since then, the hypothesis as it relates to food has been extended to suggest that multiple environmental exposures, or lack thereof, induce changes (perhaps epigenetic) that result in interruption of the default immunologic state of tolerance [20].

The proposition that the immune system improves (is more properly regulated) by exposure and in particular early exposure is supported by publications such as the Learning Early about Peanut Allergy (LEAP) [27] and Enquiring About Tolerance (EAT) [2] studies. And the idea of early oral tolerance induction has resulted in significant changes in infant feeding recommendations given by pediatricians especially as they relate to the timing of the introduction of new foods. Simultaneously, the dual-allergen exposure hypothesis has developed suggesting that early cutaneous exposure to food protein through a disrupted skin barrier would promote allergic sensitization, and oral exposure to food allergens especially early in life would induce tolerance [28].

The idea that early cutaneous exposure to food protein through a disrupted skin barrier leads to allergic sensitization has several lines of supporting evidence [28]. Studies have linked peanut allergy to severe atopic dermatitis in children under 5 years of age. In the initial phases of the LEAP study, severe eczema was used as criteria for identifying high-risk infants with an intermediate level of peanut sensitization for entry into the study [29]. Additional support is provided by a study by Brough indicating an exposure-response relationship between house dust peanut protein levels, positive peanut skin prick test, and allergy. In a multivariate model, the authors proposed an increase in environmental peanut exposure increased the odds of peanut skin test sensitization. And, this effect was augmented in children with a history of atopic dermatitis and especially with a history of severe AD. The authors concluded that exposure to peanut antigen in dust through an impaired skin barrier is a plausible route for peanut sensitization and allergy [30]. Additionally, a study that compared household peanut consumption with the level of peanut in the home indicated not only that ambient peanut in the home was biologically active but also that peanut consumption by each parent and their cumulative consumption correlated with levels of environmental peanut protein in the bedding. They concluded that peanut protein in household dust is a possible route of peanut sensitization [31]. In a similar study, Trendelenburg et al. investigated the hypothesis that high environmental exposure to peanut allergens may be a potent risk factor for cutaneous sensitization. They measured peanut levels of dust samples using immunoassay. They found peanut was detectable in 19 of 21 households in the eating area and/or in bed and peanut levels correlated with the reported frequency of peanut consumption [32].

In a series of studies of household peanut protein exposure, Brough et al. used a polyclonal peanut ELISA to demonstrate peanut protein levels in dust and on household surfaces [33]. Other works utilizing immunoassay of collected air found airborne peanut levels were lower than the limit of quantitation except for a brief period directly above peanuts being deshelled [34]. Brough et al. found peanut protein in wipe and dust samples from 45 homes [30]. Also, environmental peanut protein levels compared with peanut consumption assessed using a peanut food frequency questionnaire and other clinical and household factors. They concluded that an infant's environmental exposure to peanut is most likely to be due to home peanut consumption likely through dust exposure [35]. And Shroba et al. found that even in homes where peanut restriction is employed, substantial amounts of Ara h2 can be found in the collected house dust [36]. Brough et al. extended peanut dust exposure studies to demonstrate a strong and significant relationship between peanut dust levels and FLG mutations on peanut sensitization and peanut allergy [37]. Children with FLG mutations had a greater than threefold increased odds of peanut allergy compared with odds seen in children with wild-type FLG. These studies have provided evidence that early-life environmental peanut exposure provides an increased risk of peanut sensitization and allergy in children with a filaggrin mutation. These data further support a hypothesis that peanut allergy develops through transcutaneous sensitization in children with an impaired skin barrier [37].

Known Food Protein in House Dust

Several studies have documented the presence of significant peanut allergen in house dust and even in-house dust from homes that restrict peanut. Shroba et al. analyzed a total of 85 dust samples collected: 38 from homes of individuals with peanut allergy and 47 samples from homes without a peanut allergic individual. The median Ara h2 level in homes with an individual with peanut allergy was 1236 ng/g (interquartile range [IQR], 256–1342 ng/g), but the median Ara h2 level in homes without an individual with peanut allergy was 650 ng/g (IQR, 163–2201 ng/g). Surprisingly in 15 homes

that reported complete avoidance of peanut in the home, the Ara h2 levels were not significantly lower than those in homes that did not restrict peanuts. They concluded that although each family's definition of restriction may vary, there seemed to be peanut protein entering the home [36].

This evidence indicates that peanut allergen may be similar to cat allergen in that it is readily transported on the hands and clothing of exposed individuals and subsequently deposited in areas that have had no documented peanut presence. The question immediately arises as to what other food proteins are significant components of house dust. There has been at least one study into hen's egg protein levels in dust samples measured using ELISA. In 8 of 8 households, hen's egg was detectable in dust samples of eating area and bed. Forty-eight hours after intentional hen's egg consumption, hen's egg protein levels were significantly increased in both areas [38].

Oral Exposures Through Damaged Mouth, Esophagus, or Stomach

There are three natural ways humans are exposed to foreign proteins: via the skin, via the respiratory tract, via the oral and digestive tract. If cutaneous exposure leads to allergic sensitization and oral exposure leads to tolerance, the question must be asked, if oral exposure is through damaged or altered oral and esophageal tissue does it lead to sensitization? This question has only begun to be investigated and it is mostly viewed through the lens of oral desensitization. There are several studies that relate the development of EOE to oral immunotherapy. However, Lucendo et al. documented a significant publication bias in favor of such studies. These authors did calculate that new onset EOE after OIT occurs in up to 2.7% of patients with IgE-mediated food allergy [39, 40].

The pattern of food sensitivity-related EOE is similar to the pattern of food allergy. It is not known whether these foods are unusually allergenic or if they are simply the most common foods consumed. Hill et al. analyzed data from 35,528 children and adolescents to identify and characterize patients with IgE-mediated and EOE food allergy. The most common causes of EOE were milk, soy, egg, grains, and meats. And, IgE-mediated allergy to egg, milk, or shellfish was significantly associated with an EOE diagnosis [41].

Oral Allergy Syndrome

Oral allergy syndrome (OAS) is described as isolated oral symptoms caused by labile proteins in fresh fruits and vegetables that share homology with proteins in pollens [42]. Symptoms include pruritus and edema of the mouth, lips, tongue, and throat. Symptoms typically occur immediately after the ingestion of raw fruits and vegetables although could occur up to an hour later. These symptoms rarely progress to anaphylaxis [43]. Among those with allergic rhinitis, 23–76% experience OAS to at least one food. Among those with OAS, upward of 70% react to more than two foods [42].

Sensitization to inhaled pollen proteins via the respiratory tract is believed to be the initial pathogenic event. The pollen-specific IgE bind to the surface of mast cells and basophils throughout the body including the oral mucosa. Upon oral contact with related food, the IgE molecules recognize homologous epitopes of the food protein which trigger a localized release of inflammatory mediators. In most cases, the allergens are destroyed in the stomach, limiting a progression of the reaction. In contrast, allergens responsible for isolated food allergens are typically resistant to both heat and digestion and therefore have a higher potential for systemic reactions [44].

Profilins are known to be ubiquitous cross-reactive plant allergens. Sensitization to profilins can be found in 10–30% of pollen allergic patients [44]. The most common allergen is birch pollen which accounts for 70% of OAS reactions. The major birch pollen allergen Bet v 1 is the most relevant sensitizing protein [45]. Bet v 1 belongs to the pathogenesis-related (PR) protein family 10. Other members of the PR 10 family are found in apple, cherry, pear, celery, carrot, hazelnut, soy, and peanut [45]. They are highly susceptible to heating and digestion; however, activation of T cells can persist. In some adults with atopic dermatitis and birch pollen allergy, ingestion of cooked birch pollen-related foods can result in worsening eczema [44].

Not as much is known about grass and weed allergic patients as tree pollen allergic patients. Bermuda grass profilin (Cyn d 12) is known to cross-react with profilin in tomato and cantaloupes. Symptoms associated with ingestion of banana, melons, zucchini, and cucumber are related to profilin in ragweed (Amb a 8) [46].

Cross-reactive carbohydrate determinants (CCD) are the carbohydrates that act as cross-reacting antigens among various plants. Many CCDs are not thought to induce histamine release, but about 50% of individuals positive to olive protein (Ole e 1) show IgE antibodies to this carbohydrate and induce histamine release [47].

When fruit or vegetable allergy develops in the absence of pollen allergy, patients may be sensitized to nonspecific lipid-transfer protein (LTP). Sensitization to LTP is associated with higher rates of systemic reactions and with food-dependent exercise-induced anaphylaxis [44]. They are involved in plant defense and are abundant in the peel of edible plants. They have been found in peach, cherry, apple, hazelnut, orange, strawberry, and in pollen [44]. LTP is resistant to heating and digestive enzymes which can cause OAS symptoms as well as more severe symptoms. Sensitization to LTP is prevalent in Mediterranean areas where birch trees do not grow and uncommon in Central and Northern Europe where birch trees are common. In China, Mug wort (Art v 4) LTP is the primary sensitizer in patients with peach allergy [44].

Individuals with an allergy to natural latex may also exhibit symptoms with the ingestion of avocado, banana, kiwifruit, and chestnuts. Published case reports have also described a cross-reactivity between latex-cassava and latex-curry spice [48]. Those allergic to latex have about a 35% risk of reaction to at least one of these cross-reacting fruits, whereas those allergic to the same fruits only have an 11% risk of reaction to latex [42].

While this is not an all-inclusive list, these are examples of the most common allergens associated with OAS. Some patients may find OAS worsens during pollen seasons. Typically, heating the fruit will decrease the OAS symptoms; however, some of the proteins that are resistant to heating would need to be avoided. Eating foods that are canned may also limit the reaction. Peeling the offending food may also be helpful as the protein is often concentrated in the skin. Some studies have shown that subcutaneous immunotherapy improved OAS symptoms in 30% to even 84% of individuals examined [49] (Table 3).

Tropomyosin

Tropomyosin is a pan allergen that is found in shellfish, such as crustaceans (shrimp and crab) and mollusks (octopus, squid, mussels, oysters). It is also found in house dust mite (Der p 10) and cockroach (Bla g1). There is a high cross-reactivity between these allergens, which can be explained due to the amino acid sequences of these proteins being highly homologous across these different species [50]. Several studies have looked at this cross-sensitization of shrimp and sensitization to HDM and cockroach.

Wang et al. assessed 504 serum samples from the National Cooperative Inner City Asthma Study (NCICAS) comparing shrimp IgE to specific IgE of cockroach and HDM. They found a high correlation between shrimp, cockroach, and HDM. High exposure to cockroach in the bedroom and television room was significantly correlated with higher shrimp and cockroach IgE levels. In contrast, high exposure to dust mite in the home were correlated with IgE to D. farina, but not with shrimp levels [51].

Studies of correlation between shrimp and HDM were also done in Spain. Lopez-Matas et al. assessed the role of tropomyosin in mite- and shellfish-sensitized individuals using tropomyosin skin testing. Eight hundred fifty patients were included in this study and they were divided into three groups (mite allergic, shellfish allergic, and mite and shellfish allergic). They found the prevalence of tropomyosin was low in mite-sensitized patients (2.7%) and high in shellfish allergic patients (38.5%). Based on these results, the group found tropomyosin does not seem to be a relevant mite allergen in their area of Spain, which also holds true for other European countries [50]. Boquete et al., another group of researchers out of Northwest Spain, also found similar results that tropomyosin does not seem to be the main allergen involved in mite-seafood sensitization in mite-sensitized individuals [52].

In Asia, there is a high incidence of shellfish allergy, and Wong et al. also assessed the correlation between shrimp and dust mite sensitization. They hypothesize that tropomyosin from HDM is the primary sensitizer for shellfish allergies. HDM thrive in warm humid climates such as the tropical Asian environment, and they found a high prevalence of HDM allergy and IgE sensitization in the Asian population [53]. Shellfish sensitization correlation to HDM and cockroach sensitization does seem to vary among populations.

Alpha-Gal

IgE antibodies to carbohydrate epitopes are less common than to protein epitopes. In the early 2000, several reports worldwide were coming out describing tick bites giving rise to allergic reactions to mammalian meat. The causes of these reactions are IgE antibodies being made to the carbohydrate galactose-alpha-1,3-galactose (alpha-gal) [54]. An allergy to alpha-gal involves those previously tolerating mammalian meat (beef, pork, and lamb) suddenly developing anaphylaxis

Table 3 Types of pollens and foods associated with OAS [43, 56]

Pollens	Fruits	Vegetables	Nuts	Spices	Others
Birch	Apple, peach, plum, pear, cherry, apricot	Carrot, celery, parsley	Almond, peanut, hazelnut	Caraway, fennel, coriander, aniseed	Soy
Grass	Melon, cantaloupe, watermelon, orange, tomato	Potato	Peanut		
Mugwort	Peach, apple	Celery, carrot, parsley, bell pepper, cauliflower, cabbage, broccoli, onion		Caraway, fennel, coriander, aniseed, black pepper, mustard, garlic	Sunflower
Ragweed	Cantaloupe, honeydew, watermelon, banana	Zucchini, cucumber			
Latex	Kiwi, banana, peach, fig, tomato	Avocado, bell pepper, white potato	Chestnut		

Table 4 Hypothesized risk factors to the development of food allergies

Risk factor [reference]
• Maternal diet [4–6, 10, 11, 15–17]
• Barrier dysfunction of the infant's gut mucosa, including early inflammation [4, 5, 14]
• Lack of "good" gut microbiota [4, 5]
• Delayed introduction of allergenic foods [2, 8, 9, 18, 19, 21]
• Family history [11, 23, 24]
• Atopy history, early onset of atopy in the infant [1, 10, 8, 18, 19, 21, 28, 29]
• Hygiene hypothesis—"too clean of a society" [26]
• Early cutaneous exposure through disrupted skin barriers [30, 37]
• Oral exposure through damaged or altered oral and esophageal tissue [39–41]
• Environmental exposure [30–38]
• Cross reactivity with aeroallergens [42–55]

to meat, usually occurring 2–6 h after ingestion. In the USA, Platts-Mills group identified this reaction occurring more in a specific geographical region in the Southeastern states. The correlation was made that all these individuals reported a recent bite from adult or larval tick, *Amblyomma americanum* (lone star tick). In Europe, *Ixodes ricinus* has been implicated, while in Australia, the relevant tick is *Ixodes holocyclus* [55].

This type of red meat allergy is different than typical allergic reactions. Urticaria and gastrointestinal symptoms are common, but typically do not occur for at least 2 h, and typically delayed for 3–5 h [55]. Recently, it has been noted that exercise or other cofounding factors can speed up the onset of reaction. Second, the tissue source of the meat which can provide varying amounts of antigens can also alter the onset of reaction [55]. Testing for alpha-gal can be complicated. Skin prick testing to alpha-gal using beef, pork, or lamb yields small results (2–4 mm). Therefore, in vitro assays are recommended, with repeat testing every 8–12 months [55]. Some patients if they can avoid recurrence of tick bites will lose their sensitization in 1–2 years, and will be able to tolerate mammalian meats once again (Table 4).

Conclusion

With the increase in food allergy diagnosis, an understanding for the background involved in their development is critical. Research for a cure continues to be ongoing, but at this time the only treatment is avoidance and emergency medication if a reaction occurs. An explanation as to why food allergies develop is important, as without that understanding, it will be difficult to determine how prevention or a cure can be achieved. Breastfeeding and maternal diet provide the infant and fetus with exposure to potentially allergenic foods during a susceptible time. Early exposure to allergens can occur through a child's environment, via impaired skin barriers and mucosal surfaces. Later in life, food allergies can develop through aeroallergen sensitization, and involvement of other factors such as tropomyosin and alpha-gal further add to the complicated immune response. The key concerning the relationship of food exposure to sensitization remains elusive. Is there a particular time during the life of an individual when exposure produces tolerance? Is tolerance or sensitization related to a particular route of exposure? Or is sensitization related to the intensity or magnitude of exposure? Is a genetic predisposition always necessary? Continued research in all of these areas is necessary to turn hypothesis and speculation into a causative factor and cure.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval and Informed Consent This was a review article and not a study involving human subjects so IRB approval was not required.

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