

The Prevalence and Natural History of Food Allergy

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Abstract Numerous studies have demonstrated that the prevalence of food allergy is increasing. Not only are more children being diagnosed with food allergies, but studies suggest that when people outgrow their food allergies, it is taking longer than was previously thought. Studies in recent years have noted factors that may lead to a lower likelihood of developing a food allergy, including the early introduction of common food allergens, having a sufficient vitamin D level, or having a higher maternal intake of peanut early in pregnancy. Given a recent report that sensitization to common food allergens did not increase from the late 1980s/early 1990s to the mid-2000s, further studies will need to examine if the rise in food allergy prevalence is due to a change in the relationship between sensitization and clinical allergy or changes in the recognition and diagnosis of food allergy.

Keywords Food allergy · Prevalence · Natural history · Prevention · Skin prick testing · Food-specific IgE

Introduction

In recent years, many reports on the prevalence and natural history of food allergy have painted a grim picture. Numerous

studies have reported that food allergies are increasingly common, that it is taking longer to outgrow an allergy among those who develop tolerance, and that hospitalizations for food-induced anaphylaxis are increasing [1–9]. Conversely, recent studies have also provided some hope that we may be able to confront the rising prevalence of food allergy, including reports that the ingestion of common food allergens during pregnancy is associated with reduced odds of childhood allergy; that incorporation of common food allergens in the diet early in infancy may decrease the rate of clinical reactivity; and that introduction of baked milk or baked egg to the diet, when possible, may accelerate the development of tolerance to less cooked forms of these foods [10, 11•, 12•, 13, 14].

Overall, the prevalence of food allergy in children is between 3.9 and 8 % [15–18]. It is difficult to pinpoint a precise number when determining the prevalence of food allergy, as rates differ among different populations in different geographic areas and are likely higher when allergy is self-reported or based on sensitization (a positive skin prick test (SPT) or serum IgE test) as opposed to being confirmed by a physician-supervised oral food challenge (OFC). Among children with food allergies, strict avoidance can be very difficult, and accidental ingestions can result in severe, even life-threatening, allergic reactions. In a study by Gupta et al. utilizing data collected for 40,104 children, among those with food allergy, 38.7 % had a history of severe reactions [17]. Hospitalizations for food-induced anaphylaxis have increased in recent years, doubling from 1085 in 2000, a rate of 0.60 hospitalizations per 1000 total hospitalizations, to 2253 in 2009, a rate of 1.26 hospitalizations per 1000 total hospitalizations [9].

Patients with food allergy and their families frequently ask if they are likely to outgrow their food allergy. In a recent report from the Isle of Wight, a birth cohort born between 2001 and 2002 was followed prospectively for 10 years, with

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the children having clinical exams and skin prick testing at set times and oral food challenges when indicated [15]. The cumulative incidence of food hypersensitivity in the first decade of life was 6.8 % (64/947), while at 10 years of age the prevalence dropped to 3.6 % (30/827). There are several factors that can help predict the likelihood of resolution of a food allergy (Table 1). Having more severe symptoms on ingestion or having a lower eliciting dose required to bring on an allergic reaction has been associated with allergy persistence [2, 19–21]. The presence of other comorbid allergic diseases has been associated with more persistent food allergy [4, 5, 21]. Larger SPT wheal size and higher food-specific IgE levels are also associated with a more persistent food allergy phenotype (15–20) [2, 3, 5, 14, 19, 22, 23]. As will be discussed in more detail later in this paper, the likelihood of outgrowing a food allergy also relates to the particular food allergen, with children allergic to certain foods such as milk, egg, and wheat being more likely to outgrow their allergies than children with allergy to peanut or tree nuts [2–8, 24].

Specific Food Allergies

Milk Allergy

Milk allergy is the most common food allergy in young children, with prevalence rates estimated to be between 1.9 and 3 % [16, 25, 26]. In most cases, milk allergy presents in the first year of life [27, 28]. Studies from the 1980s and 1990s demonstrated the prognosis of developing tolerance to cow's milk to be good, with the majority outgrowing their allergy by 3 years of age [29, 30]. While more recent studies still report a high likelihood of resolution, they have provided less optimistic results about the timing of achieving tolerance [3, 4]. In a

large study from a US tertiary care center, 19 % developed tolerance by 4 years of age, 42 % by 8 years of age, 64 % by 12 years of age, and 79 % by 16 years of age [4]. In a multi-center longitudinal US study of 293 children with milk allergy, resolution of the allergy occurred in 53 % of subjects at a median age of 5.3 years [3]. In this study by Wood et al., several factors were identified that were inversely associated with the timing of milk allergy resolution, including the baseline milk-specific IgE level, SPT wheal size, and severity of eczema at diagnosis.

Several studies have shown that a majority of children with milk allergy can tolerate extensively heated milk [13, 31]. High temperatures break down conformational epitopes (amino acids brought into close proximity through protein folding) of milk proteins, thus reducing the allergenicity of this food for many individuals. The introduction of the extensively heated milk into the diet not only has quality-of-life benefits but also has therapeutic potential. Kim et al. reported that those who were able to tolerate baked milk products and incorporated them into the diet were significantly more likely to become tolerant to unheated milk within 5 years than the comparison group that maintained strict milk avoidance [13]. After ingested baked milk for just 3 months, subjects also had significantly decreased milk SPT wheal sizes and increases in their casein-specific IgG4 levels [31].

Egg Allergy

Egg allergy has been estimated to affect 0.5 to 2.5 % of young children [16, 17, 26, 32, 33]. Allergy to egg or being sensitized to egg is associated with increased risk of peanut and other food allergies, as well as atopic dermatitis and development of asthma [11•, 34–36]. In most cases, allergy to egg develops in the first year of life [27, 37]. The prognosis for egg allergy is generally good, though it varies by geographic region and studies in the US have reported that it is taking children longer to achieve tolerance than was previously thought [2, 5, 38]. Parents of children with egg allergy used to be advised that, in general, most children will outgrow their allergy by the early school-age years [38], but Savage et al. reported in 2007 that only 12 % of subjects with egg allergy in their large cohort achieved tolerance by the age of 6 years, 37 % by the age of 10 years, and 68 % by the age of 16 years [5]. The authors pointed out that the higher ages seen in achieving tolerance than was seen in previous studies could be due to the fact that their population was referred to a tertiary care center for their care. A more recent US-based multicenter study examining a cohort of 213 children with egg allergy demonstrated that the egg allergy resolved in about half of children at a median of 6 years of age [2]. The current estimate of egg allergy among adults is only 0.2 % [36].

Similar to children with milk allergy, the majority of children with egg allergy can tolerate extensively heated

Table 1 Factors helping to predict food allergy resolution

Factors indicating someone is less likely to outgrow a food allergy
-More severe symptoms with a past ingestion of the allergen [2, 19, 20]
-A lower eliciting dose to bring on a previous allergic reaction [21]
-The presence of other comorbid allergic diseases [2, 3]
-Larger skin prick test wheal size [2, 3, 22]
-Higher food-specific IgE levels [2, 3, 5, 14, 19, 23]
Factors indicating someone is more likely to outgrow a food allergy
-Tolerance of extensively heated milk (for developing tolerance to uncooked milk) [13]
-Tolerance of extensively heated egg (for developing tolerance to lightly cooked forms of egg) [14]
A calculator to help predict the age of resolution of milk or egg allergy can be found at http://cofargroup.org [3]

egg [14, 39]. Extensively heated egg does not include lightly cooked forms of egg such as scrambled egg or French toast but does include egg baked more thoroughly, such as in the form of a muffin. The introduction of the extensively heated egg also has therapeutic potential. In a study by Leonard et al., subjects in the active group, who were incorporating baked egg into their diets on a regular basis, were 14.6 times more likely to develop tolerance to regular egg than subjects in the comparison group who maintained strict egg avoidance [14]. Continued ingestion of baked egg has been associated with decreased SPT wheal diameters, ovomucoid- and ovalbumin-specific IgE levels, and increased ovalbumin- and ovomucoid-specific IgG4 levels [14, 39].

Peanut Allergy

In recent years, the prevalence of peanut allergy has been reported to be between 1.2 and 5 % [6, 10, 16, 40]. The variability between these studies likely reflects differences in geographic regions examined as well as the criteria used to define peanut allergy. Peanut allergy is one of the most common food allergies in children and adults, and the prevalence of this allergy appears to be increasing [1]. Sicherer et al. used a nationwide, cross-sectional, random telephone survey to compare self-reported peanut allergy in 1997, 2002, and 2008. They reported that the prevalence of peanut allergy in children younger than 18 years was 1.4 % in 2008, compared to 0.8 % in 2002 (P =not significant) and just 0.4 % in 1997 ($P<0.0001$) [1].

The average age at which children present with peanut allergy is 18 months, although older presentations, even in adulthood, are not uncommon [6, 41, 42]. This higher age of presentation compared to other common food allergens likely reflects an older age at which people try to introduce this food to their diet or a delayed presentation of peanut allergy due to cross-reactivity with pollens. The likelihood of outgrowing an allergy to peanut is far less than it is for milk or egg, though this allergy has been shown to resolve in a subset of young children whose peanut allergy manifested in infancy [6, 43, 44]. Hourihane et al. performed an oral challenge to peanut in 120 children with peanut allergy based on convincing histories of reactions and found that 22 (18 %) passed the oral challenge. Of the children who passed, the first reaction occurred at a mean of 11 months of age and the challenge was performed at a median of 5 years of age. More recently, as part of the prospective HealthNuts study in Australia, 1-year-old infants with OFC-confirmed peanut allergy ($n=156$) were followed up at 4 years of age with repeat OFCs, and it was reported that 22 % of children had resolution of the peanut allergy [44]. Children were unlikely to outgrow the allergy by the age of 4 years if

they had a peanut-specific IgE level ≥ 5.0 kU/L or an SPT response ≥ 13 mm at 1 year of age. Higher peanut-specific IgE levels have not only been associated with more persistent peanut allergy but have also been associated with more severe allergic reactions upon ingestion of peanut [45]. While the majority of peanut allergic children who become tolerant will do so early in life, there have been cases of resolution in adulthood, and patients may benefit from long-term follow-up [6]. Once a patient passes an OFC to peanut, it is important that he or she incorporates this food into the diet, as clinical reactivity to peanut has been demonstrated to recur after passing an OFC, usually in sensitized patients who do not introduce peanut into their diets after OFC [46, 47].

Tree Nut Allergy

Similar to peanut allergy, the prevalence of tree nut allergy has increased in recent years [1]. In the same nationwide survey of peanut allergy described above, Sicherer et al. compared self-reported tree nut allergy in 1997, 2002, and 2008. They found that the prevalence of tree nut allergy in children younger than 18 years was 1.1 % in 2008, compared to 0.5 % in 2002 and 0.2 % in 1997 ($P<0.0001$). While about 20 % of children outgrow peanut allergy, in the largest study on the natural history of tree nut allergy, Fleischer et al. reported that only 9 % of 101 patients with a history of prior reactions to tree nuts outgrew the tree nut allergy [7]. In this study, subjects who had tree nut-specific IgE levels below 10 kU_A/L underwent an OFC. In the 9 patients with a history of tree nut ingestion who passed OFCs and the 11 patients with a history of tree nut reactions who failed OFCs, the initial presenting allergic reaction did not predict whether or not the subject would have persistence of the tree nut allergy. Of those who passed the OFCs, 5 previously had mild reactions, 1 previously had a moderate reaction, and 3 previously had severe reactions, while among the 11 patients who failed the OFCs, 5 previously had mild reactions, 2 previously had moderate reactions, and 4 previously had severe reactions. Interestingly, severe allergic reactions to tree nuts were common in this cohort. Among 115 reactions after the ingestion of a tree nut, almost two thirds of the reactions were moderate to severe, with reactions to cashew and walnut accounting for approximately two thirds of the severe reactions.

Tree nut-specific IgE levels have been reported to be the best predictor of which patients would pass a tree nut OFC, with 63 % of children with tree nut-specific IgE levels ≤ 2 kU_A/L passing a challenge [7]. Fleischer et al. also reported that it is unlikely that many patients with tree nut allergy will outgrow their allergy if their tree nut-specific IgE levels increase to 10 to 20 kU_A/L. While some people generalize when talking about the different tree nuts, it is likely that the chance of passing an OFC to hazelnut

based on specific IgE levels differs from the other tree nuts among patients with birch pollen sensitization. In 2007, one of the commercial producers of a serum hazelnut-specific IgE test began supplementing with recombinant Cor a 1 to improve the test's sensitivity for birch-related reactions to hazelnut, resulting in frequent clinically irrelevant positive tests [48].

Wheat Allergy

Wheat allergy affects 0.3–1 % of children [16, 49, 50]. While there have not been many studies examining the natural history of wheat allergy, the prognosis for resolution is favorable [8, 24]. In a large, retrospective study from a tertiary care center, the median age of resolution of wheat allergy was 6.5 years, with 65 % becoming tolerant by 12 years of age [8]. A prospective Polish study following 50 children with positive food challenge results demonstrated that the median age of tolerance development was 6.5 years, with 76 % becoming tolerant by 18 years of age [24]. While these studies did find that the peak wheat-specific IgE level is helpful in determining the age at which tolerance develops, some children had resolution of their allergy despite high wheat-specific IgE levels [8, 24].

Food Allergy Prevention

In recent years, numerous studies have reported on factors that could lead to lower rates of food allergy (Table 2). Bunyanavich et al. used a US pre-birth cohort of 1277

mother-child pairs who were unselected for any disease to assess the association between maternal intake of common food allergens during pregnancy and childhood allergy and asthma [10]. While the prevalence of peanut allergy was high in this cohort (2.9 %, using the stringent criteria of a peanut-specific IgE ≥ 14 kU/L), they did find that higher peanut intake (each additional z score) during the first trimester of pregnancy was associated with a 47 % reduction in the odds of childhood peanut allergic reaction. This protective effect was not seen with other foods, though higher milk intake during the first trimester was associated with reduced asthma and allergic rhinitis, while higher maternal wheat intake during the second trimester was associated with reduced atopic dermatitis. Other studies reported benefits of a healthy diet in the prevention of food allergy. Allen et al. reported that vitamin D sufficiency in the first year of life may be protective against food allergy [51], while Grimshaw et al. reported that an infant diet consisting of high levels of fruits, vegetables, and home-prepared foods is associated with less food allergy by 2 years of age [52].

For decades, in order to address the increasing rates of food allergy, parents were urged to avoid exposing their children to foods such as peanut and fish early in life, under the assumption that early exposure could lead to allergic sensitization. This strategy of avoidance may actually be leading to the higher rates of food allergy. In the Learning Early about Peanut Allergy (LEAP) trial, infants age 4 months to 11 months with severe eczema, egg allergy, or both were randomly assigned to regularly consume or avoid peanuts until 60 months of age [11]. Among 530 infants with negative SPT results, the prevalence of peanut allergy at 60 months of age was significantly lower in the consumption group (1.9 %) than in the avoidance group (13.7 %, $P < 0.001$). Similarly, among those who initially had positive SPTs, the prevalence of peanut allergy was significantly lower in the consumption group (10.6 %) than in the avoidance group (35.3 %, $P = 0.004$). This study demonstrated that early introduction of peanut significantly decreased the frequency of the development of peanut allergy among children who were at high risk for peanut allergy. It is important to note that this was not a treatment study, and that peanut was only introduced in children who were not clinically reactive to peanut.

While the LEAP trial demonstrated that early introduction of peanut may be helpful in the prevention of peanut allergy, it left people wondering about the effect of early introduction of other common food allergens, such as milk, egg, fish, and wheat. In the Enquiring about Tolerance (EAT) trial, investigators randomly assigned 1303 exclusively breast-fed infants who were 3 months of age to either early introduction of six allergenic foods (peanut, cooked egg, cow's milk, whitefish, wheat, and sesame) or to exclusive breast-feeding to approximately 6 months of age [12•]. By 3 years of age, in the intention-to-treat analysis, there was no significant difference

Table 2 Possible interventions to help reduce the rates of food allergy

Food allergy prevention

- Early introduction of peanut has been shown to decrease the frequency of the development of peanut allergy among high risk children. This effect may also apply to other common food allergens, though the results are less clear [11•, 12•].
- Higher peanut intake during the first trimester of pregnancy was associated with a significant reduction in the odds of childhood peanut allergy [10].
- Vitamin D sufficiency in the first year of life may be protective against food allergy [51].

Extensively heated milk and egg

- When tolerated, incorporation of baked milk or baked egg into the diet has been shown to improve the likelihood that someone would become tolerant to unheated milk or lightly cooked egg respectively, compared to those maintaining strict milk or egg avoidance [13, 14].

Oral food challenges

- Despite high rates of sensitization without clinical reactivity, it has been reported that only 20 % of children with a parental-reported food allergy who were seen by a physician underwent an oral food challenge [54]. Physician-supervised oral food challenges can help identify patients who are sensitized without clinical consequence.

in the percentage of participants with food allergy to one or more of the six foods between the early-introduction group (5.6 %) and the standard-introduction group (7.1 %, $P=0.32$). While at first glance this could lead one to think that early introduction of all common allergens may not have the same protective effect seen with the early introduction of peanut, the lack of benefit from early introduction seemed to be due to an inability of those in the early-introduction group to adhere to the protocol. Less than half of the participants in the early-introduction group adhered to the protocol, and when a per-protocol analysis was used to analyze the data, there was a significantly lower prevalence of any food allergy in the early-introduction group (2.4 %) than in the standard-introduction group (7.3 %, $P=0.01$). In an editorial examining the EAT study, Wong points out that while the trial showed that the early introduction of these allergenic foods was safe, the low rate of adherence suggests that the introduction of such a demanding protocol is likely to be even lower in real-life settings [53]. He also raises the possibility of reverse causality, that the intention-to-treat analysis did not show a difference because parents and infants did not adhere to the protocol because eating a given food led to subtle avoidance behaviors, leading the parents to stop trying to feed the food to the infants.

Increased Reactivity or Increased Food Allergy Diagnosis?

Traditionally, the diagnosis of a food allergy is made using a combination of the clinical history and food-specific IgE testing, including skin prick testing, serum testing, or both. Unfortunately, while SPTs and specific IgE levels are sensitive tools for identifying the presence of food-specific IgE antibodies, sensitization often exists without clinical consequence. The medically supervised OFC is a very specific diagnostic test, but the procedure is time consuming, costly, and may result in a severe allergic reaction, so it is not always used to confirm the diagnosis of a food allergy. In fact, it has been reported that among children with parental-reported food allergy, only 20 % who were seen by a physician underwent an OFC [54]. This lack of OFCs leads to the possibility that as food allergy awareness rises and allergy testing is done more frequently, the diagnosis of a food allergy will increase, even among children who are not clinically reactive.

In a recent study, McGowan et al. reported the surprising finding that sensitization to common food allergens actually did not increase between the late 1980s/early 1990s and the mid-2000s among US 6–19 year olds, raising the possibility that it is increased recognition and diagnosis, rather than a true increase in IgE-mediated food allergy, that has led to the increases in self-reported and diagnosed food allergy [55•]. Using stored sera, IgE to milk, egg, peanut, and shrimp was compared between subjects from the National Health and Nutrition Examination Survey (NHANES) II, which was

conducted between 1988 and 1994, and subjects from NHANES 2005–2006. The authors found no significant changes in the prevalence of any level of milk, egg, or peanut sensitization and that shrimp sensitization at all levels actually decreased markedly. They did point out that it could be the relationship between sensitization and IgE-mediated food allergy that has changed over time, which could also account for the increases in self-reported and diagnosed food allergy.

Conclusions

Overall, there has been an increasing number of children with food allergy in recent years, and it is taking people longer to outgrow their food allergies than was previously thought. The likelihood of someone becoming tolerant of a food allergen varies for different foods. Most children will outgrow milk, egg, or wheat allergy, while the majority of children will not outgrow an allergy to peanut or a tree nut. Factors that make it more likely that a food allergy will persist include having a larger SPT wheal size or higher food-specific IgE level, having other comorbid allergic diseases, having more severe symptoms on ingestion, and having a lower eliciting dose required to bring on an allergic reaction. As food allergy awareness increases and people pursue more testing for food allergy, it is important to keep in mind that sensitization to a food frequently does not correlate with clinical reactivity and that OFCs may be needed to better evaluate a food allergy and avoid unnecessary dietary restrictions.

Compliance with Ethical Standards

Conflict of Interest Dr. Kattan declares no conflicts of interest relevant to this manuscript.

The author has nothing to disclose.

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

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