

The Natural History of Food Allergy

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KEY CONCEPTS

- The natural history of food allergy is generally positive.
- Natural history varies widely from one food to another.
- Peanut, tree nuts, fish, and shellfish allergies tend to be most persistent.
- Natural history varies widely for individual foods from one individual to another.
- Regular follow-up is important to monitor food-allergic patients over time.

Introduction

The natural history of food allergy refers to both the acquisition of allergic sensitivities and their natural course over time. Food allergy most often begins in the first 1–2 years of life with the process of sensitization, by which the immune system responds to specific food proteins, most often with the development of allergen-specific immunoglobulin E (IgE). Over time, most food allergy is lost, although allergy to some foods is more often long-lived. For example, while most milk and egg allergy is outgrown, most peanut and tree nut allergies are not. This chapter will review the development of food allergy and the natural history of food sensitivities over time.

When considering the natural history of food allergy, it is critical that the criteria used to define food allergy be carefully considered. Some studies report solely on rates of sensitization while others focus on clinical reactivity to specific foods. The definition of clinical reactivity is also not consistent between studies, with some relying solely on parental reports of food reactions, while others utilize food challenges and other more objective evidence of true food allergy. These details are important in that a history of an adverse food reaction, or even evidence of sensitization, does not necessarily mean that a patient will exhibit a clinical reaction upon exposure to that food. The specific criteria used to diagnose food allergy may therefore have a significant impact on the results of these studies, especially those used to measure the prevalence of food allergy.

Studies on the development of food allergy

Most food allergy is acquired in the first 1–2 years of life. The prevalence of food allergy peaks at 5–8% at 1 year of age and then falls progressively until late childhood, after which the prevalence remains stable at about 3.5% [1]. In this section studies on the development of food allergy will be reviewed.

Bock prospectively followed 480 children, recruited from a single pediatric practice, for the development of food allergy from birth through the age of 3 years [2]. Foods that were suspected of causing adverse reactions were eliminated from the diet and then reintroduced in either open or blinded challenges at regular intervals. Limited allergy testing was performed, so it was not possible to characterize the proportion of reactions that were IgE mediated. Overall, 28% of the children were reported to have an adverse food reaction and the reactions were confirmed by challenge in 8%. Eighty percent of these reactions occurred in the first year of life and the majority of the foods could be successfully reintroduced into the diet within 1 year of the onset of the allergy.

Another prevalence study was conducted in Finland in a cohort of 866 children who were followed for the occurrence of food allergy at ages 1, 2, 3, and 6 years [3]. The diagnosis of food allergy was based on a history of either rash or vomiting and all suspected reactions were confirmed by elimination and home re-challenge. Allergy testing was not otherwise conducted. Based on these criteria, the prevalence of adverse food reactions was 19% at age 1, 22% at age 2, 27% at age 3, and 8% at age 6 years. In order of prevalence, the foods most commonly implicated at all ages were citrus fruits, tomato, egg, strawberry, and fish.

An even larger cohort study was recently conducted in Norway [4–6]. For the first part of the study, a population-based cohort of 3623 children was followed from birth until the age of 2 years [3], during which parents completed questionnaires regarding adverse food reactions at 6-month intervals. The cumulative incidence of adverse food reactions was 35% by age 2 years, with milk being the single food item most commonly incriminated at 11.6%. The duration of the reactions was overall short, with approximately two-thirds of the reactions resolving within 6 months of their onset.

In the second phase of the study, those children who had persistent complaints of milk or egg allergy underwent a more detailed evaluation at the age of 2–2.5 years [5–6], including skin testing and open and double-blind oral challenges. The point prevalence of cow's milk and egg allergy or intolerance at the age of 2.5 years were estimated to be 1.1% and 1.6%, respectively. Most milk reactions were not IgE mediated and only 33% of parental reports of adverse milk reactions were confirmed, while most egg reactions were IgE mediated and 56% of parental reports were confirmed.

Host and Halcken sought to determine the prevalence of milk allergy by prospectively following 1749 Danish children from birth through age 3 years [7]. The children were carefully evaluated by history, milk elimination, oral challenge, and skin tests or radioallergen sorbent tests (RAST). Milk allergy was suspected in 117 children (6.7%) and confirmed in 39 (2.2%). Of those, 21 had IgE-mediated allergy and the remaining 18 were classified as non-IgE mediated. All milk allergy developed in the first year of life and most of the allergic children were able to tolerate milk by age 3 years (56% by age 1, 77% by age 2, and 87% by age 3 years). All children with non-IgE-mediated allergy were tolerant by age 3, compared to 75% with IgE-mediated allergy. Also of note, of those with IgE-mediated allergy, 35% had other food allergies by age 3 and 25% had other food allergies by age 10 years [8]. Those children were also more likely to develop inhalant allergies over time.

Tariq and colleagues followed a cohort of children for the development of peanut and tree nut sensitization through the age of 4 years [9]. All children born on the Isle of Wight in a 1-year period were recruited and evaluated at ages 1, 2, and 4 years. Fifteen (1.2%) of the 1218 children were sensitized to peanut or tree nuts. Thirteen were sensitive to peanut and six had had allergic reactions to peanut (0.5% of the population), while one child each had had a reaction to hazelnuts and cashews.

One final study of importance followed the development of sensitization to common food allergens in a large cohort of children, without clinical confirmation of food sensitivity. Two hundred and sixteen children from a birth cohort of 4082 children in the Multicenter Allergy Study conducted in Germany were assessed for allergy by RAST at 1, 2, 3, 5, and 6 years of age [10]. The overall annual incidence rates for food sensitization decreased from a peak of 10% at age

1 to 3% at age 6 years. Sensitization to egg and milk were most common at all ages, followed by wheat and soy. This study also found that there was a high rate of aeroallergen sensitization in children who began with food sensitivities, especially to egg [11–12]. Remarkably, if a child had both a positive family history of allergy and an egg-specific IgE level above $2\text{ kU}_A/\text{l}$ at the age of 12 months, there was a 78% positive predictive value and a 99% specificity for the development of inhalant allergen sensitivity by the age of 3 years [11].

Several points are worth emphasizing from these studies. First, suspected food allergy is extraordinarily common in early childhood, with at least one-fourth of all parents reporting one or more adverse food reactions. Second, adverse food reactions can be confirmed in 5–10% of young children with a peak prevalence at around 1 year of age. Third, most food allergy is lost over time. And finally, children who begin with one food allergy, especially if it is IgE mediated, have a very high chance of developing additional food allergies, as well as inhalant allergies. It is therefore critical that children with food allergy be identified as early as possible, both to initiate an appropriate diet for their existing allergies and to consider preventative measures that may help to reduce their chance of developing additional food allergies, as well as asthma and allergic rhinitis.

Studies on the loss of food allergy

Most food allergy is indeed lost over time. The process of outgrowing food allergies, by which a patient becomes completely tolerant to a food that had previously caused a reaction, varies a great deal for different foods and among individual patients. In the study by Bock described above [2], almost all of the adverse food reactions had been lost by the age of 3 years. Among these, there were 11 children with confirmed milk allergy and 14 children with probable milk allergy, all of whom were able to tolerate milk by the age of 3 years. The median duration of adverse reactions to milk was in fact only 9 months. In a second study by Bock, nine children who had had severe reactions to milk, egg, and/or soy at 2–15 months of age were followed for 3–9 years [13]. Over time, three of the nine children were able to fully tolerate the offending food, four could tolerate small amounts, and two continued to have reactions with small exposures.

Dannaeus and Inganas followed 82 children between the ages of 6 months and 14 years with a variety of food allergies for a period of 2–5 years [14]. Of the 12 children who were allergic to milk, 4 developed complete tolerance, 7 had reduced sensitivity, and only 1 remained unchanged by the completion of their follow-up. Fifty-five children had egg allergy, of whom 20 developed complete tolerance, 24 had reduced sensitivity, and 11 remained unchanged. The results were very different for fish and peanut/tree nut allergy, with only 5 of 32 patients with fish allergy and 0 of 35 patients with peanut or tree nut allergy developing tolerance.

Sampson and Scanlon followed a group of 75 patients between the ages of 3 and 18 years with atopic dermatitis and food allergy that had been diagnosed by skin testing, RASTs, and double-blind, placebo-controlled food challenges (DBPCFCs) [15]. Patients were re-challenged yearly to each of the foods that had previously elicited a positive challenge and after 1 year, 19 of the 75 had lost all food allergy, including 15 of 45 patients allergic to one food and 4 of 21 allergic to two foods. A total of 38 of 121 specific food sensitivities had been lost after 1 year. After 2 years, an additional 4 of 44 patients lost their food allergy, while none of the 20 patients re-challenged after 3 years had a negative challenge. The results for specific foods after 1–2 years of follow-up are represented in Table 37.1, showing that egg allergy had been lost in 24%, milk in 19%, soy in 50%, wheat in 33%, and peanut in 20%. In a similar study by Sampson, follow-up data was provided on 40 of 113 patients with food allergy and atopic dermatitis

Table 37.1 The persistence or loss of specific food sensitivities over 1–2 years in children with atopic dermatitis

Allergen	Total	Challenge	
		Positive	Negative
Egg	59	45 (76%)	14 (24%)
Milk	21	17 (81%)	4 (19%)
Soy	10	5 (50%)	5 (50%)
Wheat	6	4 (67%)	2 (33%)
Peanut	10	8 (80%)	2 (20%)
Other	15	5 (33%)	10 (66%)

Reproduced from Dannaeus A and Inganas M [14], with permission from Blackwell Publishing.

Table 37.2 Studies on the natural history of milk allergy

Author (reference)	N	Age at diagnosis	Duration of follow-up	Percent tolerant at completion of study	
				IgE-mediated (or immediate-type) reactions	Non-IgE-mediated (or delayed-type) reactions
Dannaeus [14]	47	14 days to 20 months	6 months to 4 years (mean 28 months)	29%	74%
Host [6]	39	0–12 months	Up to age 3 years	76%	100%
Hill [19]	47	3–66 months	6–39 months (mean 16 months)	40%	38%
Bishop [21]	100	1–98 months (median 16 months)	5 years	67%	86%*
Hill [22]	98	4–100 months (median 24 months)	6–73 months (mean 24 months)	22%	59%
James [26]	29	3–14 years (median 3 years)	3 years	38%	NA
Saarinen [23]	116	Mean 7 months	Up to 8.6 years	85%	100%
Skripak [24]	807	1–209 months (median 13 months)	4–285 months (median 55 months)	19% at age 4, 42% at age 8, 79% at age 16	NA

*Combines immediate and late reactors.

1–2 years after their original diagnosis [16]. In that study, egg allergy had been outgrown in 14 of 20 patients (30%), compared to 4 of 7 with milk allergy (57%), 1 of 4 with wheat allergy (25%), and 2 of 3 with soy allergy (67%).

Shek *et al.* monitored food-specific IgE levels in 88 patients with egg allergy and 49 patients with cow's milk allergy (CMA) who also underwent repeated double-blind, placebo controlled [17]. Twenty-eight of the 66 egg-allergic and 16 of the 33 milk-allergic patients lost their allergy over time. For egg, the decrease in serum IgE (sIgE) levels was significantly related to the probability of developing clinical tolerance, with the duration between challenges having an influence. For milk, there was also a significant relationship between the decrease in sIgE levels and the probability of developing tolerance to milk but no significant contribution with regard to time. Stratification into two age groups, those below 4 years of age and those above 4 years of age at the time of first challenge, had an effect, with the younger age group being more likely to develop clinical tolerance in relation to the rate of decrease in sIgE. The median food sIgE level at diagnosis was significantly less for the group developing tolerance to egg, and a similar trend was seen for milk allergy ($p=0.06$).

Milk allergy

The natural history of milk allergy has been most extensively studied [18–27]. However, as summarized in Table 37.2, the results of these studies do not provide a completely clear and consistent picture.

Dannaeus and Johansson followed 47 infants with milk allergy for 6 months to 4 years [19]. In children with immediate-type, IgE-mediated reactions, 29% developed complete tolerance to milk over the course of the study,

compared to 74% of those with delayed-type, non-IgE-mediated reactions. The trend for non-IgE-mediated milk allergy to be outgrown more quickly than IgE-mediated allergy has been demonstrated in most studies, including the study by Host and Halken [7], in which the vast majority of all children were milk tolerant by age 3 years.

A series of studies on milk allergy have been published by Hill and colleagues [20–23]. In their first natural history study [20], 47 children from 3 to 66 months of age with challenge-confirmed milk allergy were followed for a median of 16 months (range 6–39 months). Overall, 38% of the children were able to tolerate milk by the completion of the study. When the children were divided into groups based on having immediate, intermediate, or late milk reactions, tolerance occurred in 40%, 42%, and 25%, respectively. Milk-specific IgE, IgA, IgM, and IgG levels were measured and no specific immunologic changes were clearly associated with the development of milk tolerance.

In the second study from this group, a cohort of 100 children with challenge-confirmed milk allergy were followed for 5 years [22]. Overall, milk tolerance had occurred in 28% of patients by age 2, 56% by age 4, and 78% by age 6 years. When the children were again divided into groups based on having immediate, intermediate, or late reactions, tolerance had occurred by the completion of the study in 67%, 87%, and 83%, respectively. Adverse reactions to other foods were also common in this cohort, occurring to egg in 58%, soy in 47%, and peanut in 34%. Most children also developed one or more other atopic diseases, such that at the completion of the study 40% had asthma, 43% had allergic rhinitis, and 21% had eczema.

A final study from this group followed 98 children with milk allergy for a median of 2 years (range 6–72 months) [23]. In this study, the children were divided into two groups: 69 had IgE antibodies to milk with immediate-type reactions and 29 had delayed-type reactions. Over the period of follow-up, 15 of 69 (22%) with IgE-mediated disease developed tolerance, compared to 17 of the 29 (59%) with non-IgE-mediated reactions. For those children with IgE-mediated milk sensitivity, the development of tolerance was associated with lower milk-specific IgE levels at the time of diagnosis and at study completion, as well a significant reduction in their milk skin test reactivity. However, it is also important to note that 8 of the 15 who developed tolerance still had strongly positive skin tests at that time.

In the largest prospective study to date, Saarinen *et al.* followed 118 children diagnosed with milk allergy from a birth cohort study of over 6000 children [24]. Eighty-six (73%) had IgE-mediated milk and of those, 51% had become tolerant by age 2 years and 85% were tolerant at age 8.6 years. All children with IgE-negative CMA were tolerant by age 5.0 years. By age 8.6 years, children with IgE-positive CMA more frequently had asthma, rhinoconjunctivitis, atopic eczema, and sensitization to any allergen

than control subjects. They concluded that IgE-mediated milk allergy often persists to school age and is a risk factor for other atopy, while non-IgE-mediated milk allergy is a benign infantile condition.

In the largest overall study to date, our group retrospectively collected data on 807 patients with IgE-mediated milk allergy [25]. Patients were considered to have become tolerant if they passed a challenge, or experienced no reactions in the past 12 months and had a cow's milk IgE level $<3 \text{ kU}_A/\text{l}$. Using that definition, the rates of resolution were 19% at age 4, 42% by age 8, 64% by age 12, and 79% by age 16 years. Patients with persistent allergy had higher cow's milk IgE levels at all ages up to age 16 years. The highest cow's milk IgE for each patient, defined as "peak" CM-IgE, was found to be highly predictive of outcome. Of note, some patients developed tolerance during adolescence, indicating that follow-up and re-evaluation of CMA patients is an important component of their care.

Three additional studies have focused specifically on the immunologic changes associated with the development of milk tolerance. From a group of 80 milk-allergic children, James and Sampson reported on a subset of 29 who were followed for a minimum of 3 years [27]. Evaluations included annual DBPCFCs, skin tests, and measurement of casein-specific and β -lactoglobulin-specific IgE, IgG, IgG1, and IgG4 antibody concentrations. All children had specific IgE to milk as well as positive skin tests and 80% had atopic dermatitis. The median age at the time of study entry was 3 years with a range from 1 month to 11 years. Of the 29 children, 11 (38%) developed tolerance at a median age of 7 years. In those who became tolerant to milk, specific IgE and IgE/IgG ratios to both milk proteins were lower initially and decreased significantly over time.

Two even more detailed studies on antibody responses to milk proteins and the development of milk tolerance were reported by Chatchatee *et al.* [28,29]. In the first study, IgE- and IgG-binding epitopes on α_{s1} -casein were identified using the sera of 24 milk-allergic children, and the patterns of epitope recognition were analyzed to determine if they might help predict the natural history of milk allergy. When comparing epitope recognition of patients with persistent milk allergy to younger children likely to outgrow their allergy, they found that two IgE-binding regions were recognized by all of the older children with persistent milk allergy but none of the younger children. In the second study, a similar analysis was performed of IgE- and IgG-binding epitopes on β - and κ -casein in milk-allergic patients. Three IgE-binding regions on β -casein and six on κ -casein were recognized by the majority of patients in the older age group but none of the younger patients. In addition to a more clear definition of the antibody responses to specific milk proteins/epitopes, these studies suggest that it may eventually be possible to develop clinical tests, in essence epitope-specific IgE levels that may help to identify children at risk for more persistent milk allergy.

A summary of studies on the natural history of milk allergy is presented in Table 37.2. As one examines this information, a somewhat confusing picture emerges. For example, in the study by Host and Halken [7], which in many ways is the best study on milk allergy yet performed, 76% of those with IgE-mediated milk allergy and 100% of those with non-IgE-mediated milk allergy were milk tolerant by the age of 3 years. These numbers are far higher than those presented in the other studies. The only numbers that approach those are from the study by Bishop *et al.* [21], although it took until age 6 for 78% of those children to become milk tolerant. The differences in these studies are almost certainly a result of selection biases. The study by Host and Halken was a population-based study that would therefore include all degrees of milk sensitivity, whereas the other studies included children who were under the care of an allergy specialist, indicating that they may have had a more severe form of milk allergy. For the primary care physician, it is therefore likely that the more optimistic numbers will be correct, while the allergist might expect a slower rate of loss of milk allergy in their patients over time, as well as a higher percentage of patients with persistent milk allergy.

Egg allergy

Only two studies have specifically focused on the natural history of egg allergy. Ford and Taylor followed 25 children from 7 months to 9 years of age (median 17 months) with challenge-confirmed egg allergy for 2–2.5 years [30]. Egg allergy resolved in 11 of 25 (44%) and persisted in the other 14. Skin tests were negative or diminished in size in those who lost their egg reactivity compared to those with ongoing reactivity. This is similar to the 36% of children in the Dannaus study [14] who became egg tolerant, although they also reported that an additional 44% had become less sensitive over time. The largest and most recent prospective study of the natural history of egg allergy is from a Spanish cohort of 58 children, in which 50% of egg-allergic children developed tolerance by age 4–4.5 years [31]. These data would agree with the clinical observation that a slight majority of egg allergy is outgrown by the school-age years.

Peanut allergy

Until recently, the dogma had been that peanut allergy is rarely, if ever, outgrown and studies had in fact suggested that that was the case. For example, Bock followed 32 children, 1–14 years of age, with challenge-confirmed peanut allergy over a period of 2–14 years and found that 24 had had accidental peanut exposures/reactions and no patients appeared to outgrow their allergy [32].

Evidence that a subset of children with peanut allergy may indeed lose their sensitivity was first reported by Hourihane *et al.* [33]. They evaluated 230 children with a diagnosis of peanut allergy and performed oral challenges in 120. A total

of 22 children between the ages of 2 and 9 years had a negative challenge, equaling 18% of those challenged or 9.8% of the total group. They found that a negative challenge was associated with a smaller skin test size and fewer allergies to other foods compared to those with persistent peanut allergy.

Spergel *et al.* retrospectively reviewed 293 patients with a diagnosis of peanut allergy [34]. All families were offered a peanut challenge to confirm their diagnosis and a total of 33 children between the ages of 18 months and 8 years with a convincing history of peanut allergy and a positive skin test were actually challenged. Of those, 14 passed their challenge and were felt to have resolved their peanut allergy. None of the 5 patients with a history of peanut anaphylaxis developed tolerance, compared to 9 of 17 with a history of urticaria and 4 of 10 with a history of atopic dermatitis. In addition, those developing tolerance had significantly smaller skin test responses than the 19 with a positive challenge.

Skolnick *et al.* performed a detailed evaluation of 223 children with a diagnosis of peanut allergy [35], including an oral peanut challenge in those who had not had a reaction in the past year and who had a peanut-specific IgE (PN-IgE) $<20\text{ kU}_A/\text{l}$. As shown in Table 37.3, 97 children were not challenged because they were considered to still be peanut allergic based on either a history of a recent reaction or a PN-IgE level $>20\text{ kU}_A/\text{l}$ [36], and an additional 41 children were eligible to be challenged but declined. Of the 85 children who were challenged, 48 (21.5% of the total group) passed the challenge and were felt to have outgrown their peanut allergy. The PN-IgE level as measured by UniCap® (Phadia; Uppsala, Sweden) was the best predictor of a negative challenge, with 61% of those with a PN-IgE level $<5\text{ kU}_A/\text{l}$ and 67% with a level $<2\text{ kU}_A/\text{l}$ passing their challenge. The presence of other atopic diseases and the severity of initial peanut reactions did not predict the probability of losing peanut allergy, and even one patient who had had severe anaphylaxis with his initial reaction outgrew his allergy.

A final study on the natural history of peanut allergy was reported by VanderLeek *et al.* [37]. Eighty-five children with peanut allergy were studied, including 55 who were followed for at least 5 years. Among those patients, 58% who had been followed for 5 years and 75% who had been followed for at least 10 years had had at least one reaction due to an accidental exposure. In addition, the majority of these reactions were more severe than initial reactions and 52% included potentially life-threatening symptoms. Severe reactions were associated with higher PN-IgE levels compared to those with purely cutaneous reactions. The only positive note from this study was that four children did outgrow their peanut allergy.

Peanut allergy is therefore likely to be lifelong for most but not all patients. Given the fact that a substantial minority of patients do appear to lose their sensitivity over time, it is appropriate to re-evaluate children with peanut allergy on

Table 37.3 Characteristics of patients with persistent and resolved peanut allergy

	Passed challenge (N = 48)	Failed challenge (N = 37)	Unable to be challenged (N = 97)	Refused challenge (N = 41)	Total (N = 223)
Age at diagnosis					
Range	8 months to 12 years	6 months to 4 years	2 months to 10 years	8 months to 15 years	2 months to 15 years
Median (year)	1.5	1.5	1.5	2	1.5
Current age (year)					
Range	4 to 17.5	4 to 13	4 to 20	4 to 16.5	4 to 20
Median	6	6.5	7	7	6.5
PN-IgE at diagnosis*					
Range	<0.35 to 52.9	1.8 to 24.4	4.5 to >100	0.64 to >100	<0.35 to >100
Median	2.2	2.91	>100	6.27	19.8
Current PN-IgE*					
Range	<0.35 to 20.4	<0.35 to 18.2	16.8 to >100	<0.35 to 16.9	<0.35 to >100
Median	0.69	2.06	>100	4.98	10.7

PN-IgE refers to peanut-specific IgE level in kU_A/l. A level <0.35 is considered negative and any level over 100 is reported as >100.
Reproduced from Ford RPK and Taylor B [30], with permission from the BMJ Publishing Group.

a regular basis. Those patients who have not had reactions in the past 1–2 years and who have a low PN-IgE level should be considered for an oral challenge in a supervised setting. If a patient is still peanut allergic by late childhood or adolescence, it is very unlikely that they will subsequently lose their allergy and regular retesting may no longer be warranted.

One additional issue in the natural history of peanut allergy relates to the potential for the recurrence of the allergy in some patients with resolved peanut allergy.

Busse *et al.* first reported such recurrences and estimated a recurrence rate of 14% after 3 of their 21 patients had recurrences [38]. Each of these patients reported consuming peanut intermittently in small amounts after passing a food challenge to peanut, and then reacquired their allergy 1–2 years later. Next, Fleischer *et al.* surveyed 64 patients who had outgrown their peanut allergy to see whether patients ate peanut products since passing their challenge, what types of peanut-containing foods they ate, and how frequently they ate them, and whether there were any allergic reactions to peanuts [39]. They found that although 97% had eaten peanut since passing their challenge, ongoing aversion to peanut is common, with 70% of patients eating peanut infrequently and in small amounts. Two of the 64 patients had suspicious allergic reactions to peanut.

Because of concerns that more patients might have had recurrences and did not know it because of their ongoing peanut avoidance, Fleischer *et al.* invited all patients from their center who had outgrown peanut allergy to undergo re-evaluation, including questionnaires, skin tests, peanut-specific IgE levels, and DBPCFCs [40]. Of 68 patients, 47 continued to tolerate peanut, of which 34 ingested concentrated peanut products at least once per month and 13 ate peanut infrequently or in limited amounts but passed a DBPCFC. The status of 18 patients was indeterminate

because they ate peanut infrequently or in limited amounts and declined to have a DBPCFC. The overall recurrence rate was 7.9 (95% CI 1.7–21.4%). They concluded that children who outgrow peanut allergy are at risk for recurrence, and this risk is significantly higher for patients who continue to largely avoid peanut after resolution of their allergy. Based on these findings, they recommended that patients eat peanut frequently and carry epinephrine indefinitely until they have demonstrated ongoing peanut tolerance.

Tree nuts allergy

The study by Dannaeus [14] did include 26 patients with tree nut allergy, none of whom lost their sensitivity in a 2–5 year follow-up. Our group evaluated 278 patients with tree nut allergy, defined as a history of reaction on ingestion and evidence of tree nut-specific IgE or positive tree nut-specific IgE level but no history of ingestion [41]. If all current tree nut-specific IgE levels were <10kU_A/l, DBPCFCs were offered. One hundred and one of the 278 (36%) had a history of acute reactions, 12 (12%) of whom had reactions to multiple tree nuts and 73 (63%) of whom had a history of moderate-to-severe reactions. Nine of 20 patients who had previously reacted to a tree nuts passed challenges, so that 9 (8.9%; 95% CI, 4–16%) of 101 patients with a history of prior tree nut reactions outgrew their allergy. Fourteen of 19 who had never ingested tree nuts but had detectable tree nut-specific IgE levels passed challenges. One hundred and sixty-one did not meet the challenge criteria, and 78 met the criteria but declined challenges. Fifty-eight percent with tree nut-specific IgE levels of 5kU_A/l or less and 63% with tree nut IgE levels of 2kU_A/l or less passed challenges. We concluded that approximately 9% of patients outgrow tree nut allergy, including some who had prior severe reactions.

Other foods

Far less has been published about the natural history of other food allergies. Among the other most common food allergens, it is clinically recognized that soy and wheat allergy are typically outgrown in the pre-school-age years, but no large studies have focused on the natural course of these food allergies. In the studies by Sampson of children with food allergy and atopic dermatitis (1516), soy allergy was outgrown in 50% and 67% of children over a 1–2 year follow-up, compared to 25% and 33% for wheat. The few children in the studies of Bock [2] and Host [7] who had soy and wheat allergy had lost these allergies by the age of 3 years. Hill *et al.* did report on 18 infants with intolerance to both soy and extensively hydrolyzed infant formulas through the age of 3 years [42]. However, while they report that two children were tolerant of soy by age 3 years, the true frequency of soy tolerance could not be determined since soy had still not been reintroduced to 13 children at the completion of the study.

As was noted above in a number of studies, adverse reactions to fruits, vegetables, and other cereal grains are typically very short-lived [2–3,14]. While some children do have severe, IgE-mediated allergies to these foods that may persist over time, for most children they can be successfully reintroduced into the diet within a period of 6–12 months. Many of these may in fact represent intolerances or irritant reactions than true allergy as well.

On the contrary, although actual studies are limited, it has been appreciated that allergies to fish, shellfish, and seeds are usually not outgrown. The study by Dannaeus [14] did include 32 children with fish allergy, of whom 5 became tolerant. One additional study followed 11 patients with shrimp allergy over a 2-year period and found that there were no significant changes in allergen-specific antibody levels over that period of time [43].

Food allergy in adults

Most study on the natural course of food allergy has logically involved children. The most common food sensitivities in adults include peanut, tree nuts, fish, and shellfish, all of which are most often lifelong. In fact, it is their persistent nature that makes them the most common food allergies in adults, in that most of these allergies are actually acquired in childhood and persist into adulthood.

One study, however, did focus on the natural history of food allergies in adults [44]. Twenty-three adults with allergies to a variety of foods underwent baseline DBPCFCs, in which clear reactions in 10 patients to a total of 13 food were identified. They were then placed on strict dietary avoidance of the offending food for 1–2 years and re-challenged. Five (38%) of the 13 previously offending foods were well tolerated, including milk in two patients

and wheat, egg, and tomato in one patient each. The two patients with nut allergy continued to react, as did two patients with milk allergy and one patient each with allergies to potato, garlic, and rice.

Follow-up of the food-allergic child

It is imperative that food-allergic children undergo regular follow-up. This is necessary to monitor growth, signs, and symptoms of ongoing food allergy, adherence to the recommended avoidance diet, and objective measures of food allergy. Any reactions that have occurred need to be reviewed with particular attention to how the reaction might have been prevented and whether the treatment provided was appropriate.

All children with food allergy should also be re-evaluated at regular intervals to determine if the allergy has been outgrown. This typically should be done annually, although for some food allergies a shorter or longer interval might be appropriate. For example, an infant with adverse reactions to fruits or vegetables might deserve re-evaluation after 3–6 months whereas an older child who clearly has persistent peanut or tree nut allergy may no longer need repeat testing, although regular follow-up is still important to review avoidance procedures and treatment protocols.

The re-evaluation process may include skin testing, measurement of specific IgE levels, and/or oral food challenges, depending on the specific clinical scenario. It is very important to note, however, that a positive skin test or IgE level does not necessarily mean that the food allergy has not been outgrown, since these tests can remain positive even when the patient is no longer clinically sensitive. Quantitative IgE levels (e.g. UniCAP® or CAP System FEIA®) have increasingly become the test of choice to monitor food allergies over time and to help guide decisions about the timing of oral food challenges. In the end, a food challenge will usually be necessary to prove that an allergy has been outgrown. These must be performed with caution because severe reactions may at times occur even when the testing suggested that the food allergy had most likely been outgrown.

Until an allergy has been outgrown, it is recommended that a strict avoidance diet be maintained. However, while the clinical impression has been that strict avoidance increases the chance of outgrowing a food allergy and may even hasten the process, there is very little data to support this notion [27,44]. In addition, it is clear that some children rapidly outgrow their food allergies without strict avoidance while others who fail to lose their allergies even with the most stringent diet. Since strict avoidance is so difficult, it would be ideal if we could somehow identify, such as with epitope mapping, those children who might be equally likely to outgrow their food allergies with or without a strict diet. However, until we have further information on this issue, it is still likely that the majority

of children with food allergy will benefit from very strict avoidance, at least to avoid symptoms and hopefully to promote the outgrowing process.

Conclusions

An understanding of the natural history and prevention of food hypersensitivity is extremely important to the management of food-allergic patients. Although the various studies on these topics are not completely consistent, there are trends in the data that provide several clear messages. First, food allergy is very common. Second, the vast majority of food allergy has its onset in the first 1–2 years of life. Third, most food allergy is outgrown, although there are notable exceptions to this generally positive outcome. Fourth, food allergy is often the first of the atopic diseases, with most children going on to develop respiratory allergies over time. Finally, at least some food allergy can be prevented by avoiding major food antigens in infancy and early childhood.

It is also important to stress the importance of making early, accurate diagnoses of childhood food allergy. Only this will allow for the initiation of the key elements necessary for the care of the food-allergic patient, including education about avoidance diets and the development of emergency care plans for the treatment of allergic reactions. Avoidance diets are complex and require detailed education, without which the child will be at risk for accidental reactions and possibly even more persistent food allergy. In addition, measures that might help to prevent the development of additional food allergies, as well as inhalant allergies, should be initiated at the time of the initial diagnosis.

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