

The Natural History of Food Allergy

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ABSTRACT. The natural history of food allergy refers to the development of food sensitivities as well as the possible loss of the same food sensitivities over time. Most food allergy is acquired in the first 1 to 2 years of life, whereas the loss of food allergy is a far more variable process, depending on both the individual child and the specific food allergy. For example, whereas most milk allergy is outgrown over time, most allergies to peanuts and tree nuts are never lost. In addition, whereas some children may lose their milk allergy in a matter of months, the process may take as long as 8 or 10 years in other children. This review provides an overview of the natural history of food allergy and provides specific information on the natural course of the most common childhood food allergies. *Pediatrics* 2003;111:1631–1637; food allergy, cow milk allergy, egg allergy, peanut allergy, natural history, prevalence, tolerance.

ABBREVIATIONS. IgE, immunoglobulin E; RAST, radioallergen sorbent test; DBPCFC, double-blind, placebo-controlled food challenge; PN, peanut-specific.

Questions about food allergy occur daily in pediatric practice, and an understanding of the natural history of food allergy—and atopy in general—is therefore extremely valuable. Any discussion of the natural history of food allergy must include information on both the acquisition of allergic sensitivities and their natural course over time. Food allergy most often begins in the first 1 to 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). Once sensitized, the allergic individual may experience an adverse reaction on exposure to a sufficient dose of that food. Over time, most food allergy is lost, although allergy to some foods is more often long-lived. For example, whereas most milk and egg allergy is outgrown, most peanut and tree nut allergies are not.

This review details the results of studies on both the development of food allergies and their natural history over time. In the examination of these studies, it is critical that the criteria used to define food allergy be carefully considered. Some studies report solely on rates of sensitization, whereas others focus on clinical reactivity to specific foods. The definition

of clinical reactivity is also not consistent between studies in that some rely solely on parental reports of food reactions, whereas others use 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 on 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 to 2 years of life. The prevalence of food allergy peaks at ~6% to 8% at 1 year of age and then falls progressively until late childhood, after which the prevalence remains stable at 1% to 2%. In this section, studies on the development of food allergy are reviewed.

Bock¹ prospectively followed 480 children, recruited from a single pediatric practice, for the development of food allergy from birth through the age of 3 years. 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 9 to 12 months of the onset of the allergy.

Another prevalence study was conducted in a cohort of 866 Finnish children who were followed for the occurrence of food allergy at ages 1, 2, 3, and 6 years.² 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 rechallenge. Allergy testing was not otherwise conducted. On the basis of these criteria, the prevalence of food allergy was determined to be 19% at age 1, 22% at age 2, 27% at age 3, and 8% at age 6. In order of prevalence, the most common food allergens at all ages were citrus fruits, tomato, egg, strawberry, and fish. These results are interesting, but the extremely high prevalence rates raise concern that the diagnostic methods may have overestimated the true occur-

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rence of food allergy and that many of the adverse reactions to foods such as citrus fruits and tomato may have represented more contact reactions than true allergy.

An even larger cohort study was recently conducted in Norway.³⁻⁵ For the first part of the study, a population-based cohort of 3623 children were followed from birth until the age of 2,³ during which parents completed questionnaires regarding adverse food reactions at 6-month intervals. Information was available at all age points for 77.4% of the families, and the cumulative incidence of adverse food reactions was 35% by age 2. Fruits, milk, and vegetables accounted for nearly two thirds of all reported reactions, with milk being the single food item most commonly incriminated with a cumulative incidence 11.6%. The cumulative incidences of reported reactions to fruits and vegetables were 20.4% and 7.3%, respectively, with citrus fruits, strawberry, and tomatoes the most common food items in these groups. The cumulative incidences were lower for reactions associated with egg (4.4%), fish (3%), nuts (2.1%), and cereals (1.4%). The duration of the reactions overall was short, with approximately two thirds of the reactions resolving within 6 months of their onset.

In the second phase of the study, 2721 children from the original cohort who had persistent complaints of milk or egg allergy underwent a more detailed evaluation at the age of 2 to 2.5 years,^{4,5} including skin testing and open and double-blind oral challenges. The point prevalence of cow milk allergy or intolerance at the age of 2.5 years was estimated to be 1.1%, although this was believed to be an underestimation in that several unrecognized reactions were detected. Most milk reactions were not IgE mediated, and only one third of parental reports of adverse milk reactions were confirmed. The point prevalence of egg allergy at the same age was 1.6%. Of note, most reactions to egg were IgE mediated, very few egg reactions were unrecognized, and 56% of parental reports of egg allergy were confirmed.

Host and Halken⁶ sought to determine the prevalence of milk allergy by prospectively following 1749 Danish children from birth through age 3. The children were carefully evaluated by history, milk elimination, oral challenge, and skin tests or radioallergosorbent tests (RASTs). Milk allergy was suspected in 117 (6.7%) children 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 by age 3 most of the allergic children were able to tolerate milk. In fact, 56% were milk tolerant by age 1, 77% by age 2, and 87% by age 3. All children with non-IgE-mediated allergy were tolerant by age 3, compared with 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 at age 10.⁷ Those children were also more likely to develop inhalant allergies over time.

Tariq et al⁸ followed a cohort of children for the development of peanut and tree nut sensitization

through the age of 4 years. All children born on the Isle of Wight in a 1-year period were recruited and evaluated at ages 1, 2, and 4 years. Of the 1456 children originally included, 1218 were reviewed at age 4; of these, 981 had skin testing performed. Fifteen (1.2%) of the 1218 children were sensitized to peanut or tree nuts. Thirteen were sensitive to peanut, and 6 had had allergic reactions to peanut (0.5% of the population); 1 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. A total of 216 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.⁹ The overall annual incidence rates for food sensitization decreased from a peak of 10% at age 1 to 3% at age 6. 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.^{10,11} Remarkably, if a child had both a positive family history of allergy and an egg-specific IgE level above 2 kU_A/L at the age of 12 months, then there was a 78% positive predictive value and 99% specificity for the development of inhalant allergen sensitivity by the age of 3 years.¹⁰

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 1 or more adverse food reactions. Second, true food allergy can be confirmed in 5% to 10% of young children with a peak prevalence at ~1 year of age. Third, as is discussed in detail in the next section, most food allergy is lost over time. Finally, children who begin with 1 food allergy, especially if it is an IgE-mediated allergy, 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 institute preventive 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

Thankfully, 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. It is also important to note that the process of outgrowing a food allergy may be helped by strict avoidance of the offending food, in that repeated exposures to even small quantities may delay the development of tolerance in some patients. The studies in this section all deal with the natural history of established food allergy over time. The first several studies deal with populations of food-allergic patients with a variety of food sensitivities; the remain-

der focuses on the natural history of single types of food allergy.

In the study by Bock¹ described above, all but 4 of the adverse food reactions had been lost by the age of 3 years. Among these 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. The median duration of adverse reactions to milk was in fact only 9 months. In a second study by Bock,¹² 9 children who had had severe reactions to milk, egg, and/or soy at 2 to 15 months of age were followed for 3 to 9 years. Over time, 3 of the 9 children were able to tolerate fully the offending food, 4 could tolerate small amounts, and 2 continued to have reactions with small exposures.

Dannaeus and Inganas¹³ followed 82 children from the ages of 6 months to 14 years with a variety of food allergies for a period of 2 to 5 years. 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, 20 of which developed complete tolerance, 24 had reduced sensitivity, and 11 remained unchanged. These results are very different from those 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 Scanlon¹⁴ 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 (DBPCFC). Patients were rechallenged yearly with each of the foods that had previously elicited a positive challenge; after 1 year, 19 of the 75 had lost all food allergies, including 15 of 45 patients who were allergic to 1 food and 4 of 21 who were allergic to 2 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, whereas none of the 20 patients who were rechallenged after 3 years had a negative challenge. The results for specific foods after 1 to 2 years of follow-up are represented in Table 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 and McCaskill,¹⁵ follow-up data were provided on 40 of 113 patients with food allergy and atopic dermatitis 1 to 2 years after their original diagnosis. In that study, egg allergy had been outgrown in 14 of 20 patients (30%), compared with 4 of 7 with milk al-

ergy (57%), 1 of 4 with wheat allergy (25%), and 2 of 3 with soy allergy (67%).

MILK ALLERGY

The natural history of milk allergy has been most extensively studied.^{16–25} Unfortunately, however, the results of these studies do not provide a completely clear and consistent picture (Table 2).

Dannaeus and Johansson¹⁷ followed 47 infants with milk allergy for 6 months to 4 years. In children with immediate-type, IgE-mediated reactions, 29% developed complete tolerance to milk over the course of the study, compared with 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 Halcken⁶ described above. It should be noted, however, that the vast majority of all children in that study were milk tolerant by age 3.

Hill et al¹⁸ in Australia published a series of studies on milk allergy.^{18–21} In their first natural history study, 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 on the basis of having immediate, intermediate, or late milk reactions, tolerance occurred in 40%, 42%, and 25%, respectively. Milk-specific IgE, immunoglobulin A (IgA), immunoglobulin M (IgM), and IgE 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.²⁰ The age at diagnosis ranged from 1 month to 8 years with a mean of 16 months. Overall, milk tolerance had occurred in 28% of patients by age 2, 56% by age 4, and 78% by age 6. When the children were again divided into groups on the basis of having immediate, intermediate, or late reactions, tolerance by the completion of the study had occurred in 67%, 87%, and 83%, respectively. It is also important to note that adverse reactions to other foods were very common, occurring to egg in 58%, soy in 47%, and peanut in 34%. Most children also developed 1 or more other atopic disease, such that by 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).²¹ In this study, the children were divided into 2 groups; 69 had IgE antibodies to milk with immediate-type reactions, and 29 had delayed-type reactions. Over the period of follow-up, 15 (22%) of 69 with IgE-mediated disease developed tolerance, compared with 17 (59%) of the 29 with non-IgE-mediated reactions. For 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 as a significant reduction in their milk skin test reactivity.

TABLE 1. Persistence or Loss of Specific Food Sensitivities Over 1–2 Years in Children With Atopic Dermatitis¹⁴

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	3 (33%)	10 (66%)

TABLE 2. Studies on the Natural History of Milk Allergy

Reference	N	Age at Diagnosis	Duration of Follow-up	% Tolerant at Completion of Study	
				IgE-Mediated (or Immediate-Type) Reactions	Non-IgE-Mediated (or Delayed-Type) Reactions
Dannaeus and Inganas ¹⁴	47	14–20 mo	6 mo to 4 y (mean 28 mo)	29%	74%
Host and Halcken ⁶	39	0–12 mo	To age 3 y	76%	100%
Hill et al ¹⁸	47	3–66 mo	6–39 mo (mean 16 mo)	40%	38%
Bishop et al ²⁰	100	1–98 mo (mean 16 mo)	5 y	67%	86%*
Hill et al ²¹	98	4–100 mo (median 24 mo)	6–73 mo (median 24 mo)	22%	59%
James and Sampson ²³	29	3–14 y (median 3 y)	3 y	38%	NA

* Combines immediate and late reactors.

However, it is also important to note that 8 of the 15 who developed tolerance still had strongly positive skin tests at that time.

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 Sampson²³ reported on a subset of 29 who were followed for a minimum of 3 years. 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 recently reported by Chatchatee et al.^{24,25} 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 whether this might be associated with the natural history of milk allergy. When comparing epitope recognition of patients with persistent milk allergy with younger children who are likely to outgrow their allergy, they found that 2 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 6 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, the truly exciting aspect of these studies is that this information may eventually lead to the development of clinical tests, in essence epitope-specific RASTs, that may help to identify children who are at risk for more persistent milk allergy.

A summary of studies on the natural history of milk allergy is presented in Table 2. As one examines

this information, a somewhat confusing picture emerges. For example, in the study by Host and Halcken,⁶ 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,²⁰ 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 Halcken was a population-based study that would therefore include all degrees of milk sensitivity, whereas the other studies were based on 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 practicing pediatrician, it is therefore likely that the more optimistic numbers will be correct, whereas 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 1 study has specifically focused on the natural history of egg allergy. Ford and Taylor²⁶ followed 25 children from 7 months to 9 years of age (median: 17 months) with challenge-confirmed egg allergy for 2 to 2.5 years. Egg allergy resolved in 11 (44%) of 25 and persisted in the other 14. Skin tests were negative or diminished in size in those who lost their egg reactivity compared with those with ongoing reactivity. This is similar to the 36% of children in the Dannaeus study¹³ who became egg tolerant, although they also reported that an additional 44% had become less sensitive over time. Those data would agree with the clinical observation that the vast majority of egg allergy is outgrown by the school-age years.

PEANUT ALLERGY

The natural history of peanut allergy has received a great deal of attention of late, primarily as a result of changes in our concept of this allergy. The teaching had been that peanut allergy is rarely or never outgrown, and studies had in fact suggested that that was the case. For example, Bock and Atkins²⁷ fol-

lowed 32 children who were 1 to 14 years of age and had challenge-confirmed peanut allergy over a period of 2 to 14 years and found that 24 had had accidental peanut exposures/reactions and no patients seemed to outgrow their allergy.

Clear evidence that a subset of children with peanut allergy may indeed lose their sensitivity was first reported by Hourihane et al.²⁸ They evaluated 230 children with a diagnosis of peanut allergy and performed oral challenges in 120. The selection of those children to be challenged was not standardized, except that those with a negative skin test or a history of tolerating peanut were offered a challenge and those with a history of life-threatening reactions were not. 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 with those with persistent peanut allergy.

Spergel et al.²⁹ retrospectively reviewed 293 patients with a diagnosis of peanut allergy. 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 believed to have resolved their peanut allergy. None of their 5 patients with a history of peanut anaphylaxis developed tolerance, compared with 9 of 17 with a history of urticaria and 4 of 10 with a history of atopic dermatitis. In addition, those who developed tolerance had significantly smaller skin test responses than the 19 with a positive challenge.

Skolnick et al.³⁰ performed a detailed evaluation of 223 children with a diagnosis of peanut allergy, 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 kU_A/L. As shown in Table 3, 97 children were not challenged because they were considered still to be peanut allergic on the basis of either a history of a recent reaction or a PN-IgE level >20 kU_A/L,³¹ 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 be-

lieved to have outgrown their peanut allergy. Since the completion of the study, an additional 7 children who originally declined to be challenged and 2 others who failed their initial challenge have now passed a challenge, such that at least 24.6% of this group of peanut-allergic children have now outgrown their allergy. The PN-IgE level as measured by CAP-RAST was the best predictor of a negative challenge, with 61% of those with a PN-IgE level <5 kU_A/L and 67% with a level <2 kU_A/L passing their challenge. The presence of other atopic diseases and the severity of initial peanut reactions did not predict the chance of losing peanut allergy, and even 1 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 Vander Leek et al.³² 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 experienced at least 1 reaction as a result of 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 with those with purely cutaneous reactions. The only positive note from this study was that 4 children did outgrow their peanut allergy.

Peanut allergy is therefore likely to be a lifelong disorder for most but not all patients. Because a substantial minority of patients do seem to lose their sensitivity over time, it is appropriate to reevaluate children with peanut allergy on a regular basis. Patients who have not had reactions in the past 1 to 2 years and who have a low PN-IgE level (≤5 kU/L) should be considered for an oral peanut challenge in a supervised setting. If a patient is still peanut allergic by late childhood or adolescence, then it is very unlikely that he or she will subsequently lose the allergy, and regular retesting may no longer be warranted.

OTHER FOODS

Far less has been published about the natural history of other food allergies. Among the other most

TABLE 3. Characteristics of Patients With Persistent and Resolved Peanut Allergy³¹

	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 mo–12 y	6 mo–4 y	2 mo–10 y	8 mo–15 y	2 mo–15 y
Median (y)	1.5	1.5	1.5	2	1.5
Current age (y)					
Range	4–17.5	4–13	4–20	4–16.5	4–20
Median	6	6.5	7	7	6.5
PN-IgE at diagnosis*					
Range	<0.35–52.9	1.8–24.4	4.5–>100	0.64–>100	<0.35–>100
Median	2.2	2.91	>100	6.27	19.8
Current PN-IgE*					
Range	<0.35–20.4	<0.35–18.2	16.8–>100	<0.35–16.9	<0.35–>100
Median	0.69	2.06	>100	4.98	10.7

* A level <0.35 is considered negative, and any level over 100 is reported as >100.

common food allergens, it is clinically recognized that soy and wheat allergy are typically outgrown in the preschool-age years, but no large studies have focused on the natural course of these food allergies. In the studies by Sampson and colleagues^{14,15} of children with food allergy and atopic dermatitis, soy allergy was outgrown in 50% and 67% of children over a 1- to 2-year follow-up, compared with 25% and 33% for wheat. The few children in the studies of Bock¹ and Host⁶ who had soy and wheat allergy had lost these allergies by the age of 3. Hill et al³³ did report on 18 infants with intolerance to both soy and extensively hydrolyzed infant formulas through the age of 3. However, although they report that 2 children were tolerant of soy by age 3, the true frequency of soy tolerance could not be determined because 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.^{1,2,13} Although 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 to 12 months. Many of these may in fact represent more intolerances or irritant reactions than true allergy as well.

On the contrary, although actual studies are limited, it has been appreciated that allergies to tree nuts, fish, shellfish, and seeds are usually not outgrown. The study by Dannaeus and Inganas¹³ did include 26 patients with tree nut allergy, none of whom lost their sensitivity in a 2- to 5-year follow-up, as well as 32 children with fish allergy, 5 of whom seemed to lose their allergy. 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.³⁴

FOOD ALLERGY IN ADULTS

Most studies on the natural course of food allergy have 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.³⁵ 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 foods were identified. They were then placed on strict dietary avoidance of the offending food for 1 to 2 years and rechallenged. Five (38%) of the 13 previously offending foods were well tolerated, including milk in 2 patients and wheat, egg, and tomato in 1 patient each. The 2 patients with nut allergy continued to react, as did 2 patients with milk allergy and 1 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 under the supervision of both their pediatrician and an allergist. 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 reevaluated by their allergist at regular intervals to determine whether 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 reevaluation after 3 to 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 reevaluation process may include skin testing, RAST analyses, and/or oral food challenges, depending on the specific clinical scenario. It is important to note, however, that a positive skin test or RAST does not necessarily mean that the food allergy has not been outgrown, because these tests can remain positive even when the patient is no longer clinically sensitive. CAP-RASTs (quantifying food-specific IgE) 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 under the direction of an allergist will usually be necessary to prove that an allergy has been outgrown. As described in the section on diagnosis, 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.

SUMMARY AND CLINICAL IMPLICATIONS

For a topic as important as this one, the available data are still limited and to some degree confusing. Despite this, however, the general patterns are clear enough to provide useful information to patients and their families about the likely course of their food allergy over the course of their childhood and beyond. Hopefully, additional study will help to clarify further some of these issues, including better laboratory markers of persistent versus transient food allergy and the true necessity for strict avoidance diets.

The issue of avoidance diets is especially troubling. Although the clinical impression has been that strict avoidance increases the chance of outgrowing a food allergy and may even hasten the process, there are very few data to support this notion.^{23,35} In addition, in practice, we certainly see some children who rapidly outgrow their food allergies without strict avoidance and others who fail to lose their allergies even with the most stringent diet. Because 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 additional information on this issue, it is still likely that the majority of children with food allergy will benefit from strict avoidance, at least to avoid symptoms and hopefully to promote the outgrowing process.

It is also important to stress once again 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 considered at the time of the initial diagnosis, especially because food allergy is often the first manifestation of allergy in early childhood.

REFERENCES

- Bock SA. Prospective appraisal of complaints of adverse reactions to foods in children during the first 3 years of life. *Pediatrics*. 1987;79:683–688
- Kajosaari M. Food allergy in Finnish children aged 1 to 6 years. *Acta Paediatr Scand*. 1982;71:815–819
- Eggesbo M, Halvorsen R, Tambs K, Botten G. Prevalence of parentally perceived adverse reactions to food in young children. *Pediatr Allergy Immunol*. 1999;10:122–132
- Eggesbo M, Botten G, Halvorsen R, Magnus P. The prevalence of CMA/CMPI in young children: the validity of parentally perceived reactions in a population-based study. *Allergy*. 2001;56:393–402
- Eggesbo M, Botten G, Halvorsen R, Magnus P. The prevalence of allergy to egg: a population-based study in young children. *Allergy*. 2001;56:403–411
- Host A, Halken S. A prospective study of cow milk allergy in Danish infants during the first 3 years of life. Clinical course in relation to clinical and immunological type of hypersensitivity reaction. *Allergy*. 1990;45:587–596
- Host A, Halken S, Jacobsen HP, Eastmann A, Mortensen S, Mygil S. The natural course of cow's milk protein allergy/intolerance. *J Allergy Clin Immunol*. 1997;99:S490 (abstr)
- Tariq SM, Stevens M, Matthews S, Ridout S, Twiselton R, Hide DW. Cohort study of peanut and tree nut sensitization by the age of 4 years. *BMJ*. 1996;313:514–517
- Kulig M, Bergmann R, Klettke U, Wahn V, Tacke U, Wahn U, and the Multicenter Allergy Study Group. Natural course of sensitization to food and inhalant allergens during the first 6 years of life. *J Allergy Clin Immunol*. 1999;103:1173–1179
- Nickel R, Kulig M, Forster J, et al. Sensitization to hen's egg at the age of 12 months is predictive for allergic sensitization to common indoor and outdoor allergens at the age of 3 years. *J Allergy Clin Immunol*. 1997;99:613–617
- Kulig M, Bergmann R, Niggemann B, Burow G, Wahn U, and the Multicenter Allergy Study Group. Prediction of sensitization to inhalant allergens in childhood: evaluating family history, atopic dermatitis and sensitization to food allergens. *Clin Exp Allergy*. 1998;28:1397–1403
- Bock SA. Natural history of severe reactions to foods in young children. *J Pediatr*. 1985;107:676–680
- Dannaeus A, Inganas M. A follow-up study of children with food allergy. Clinical course in relation to serum IgE- and IgG-antibody levels to milk, egg, and fish. *Clin Allergy*. 1981;11:533–539
- Sampson HA, Scanlon SM. Natural history of food hypersensitivity in children with atopic dermatitis. *J Pediatr*. 1989;115:23–27
- Sampson HA, McCaskill CC. Food hypersensitivity and atopic dermatitis: evaluation of 113 patients. *J Pediatr*. 1985;107:669–675
- Businco L, Benincori N, Cantani A, Tacconi L, Picarazzi A. Chronic diarrhea due to cow's milk allergy. A 4- to 10-year follow-up study. *Ann Allergy*. 1985;55:844–847
- Dannaeus A, Johansson SGO. A follow-up of infants with adverse reactions to cow's milk. *Acta Paediatr Scand*. 1979;68:377–382
- Hill DJ, Firer MA, Ball G, Hosking CS. Recovery from milk allergy in early childhood: antibody studies. *J Pediatr*. 1989;114:761–766
- Hill DJ, Firer MA, Shelton MJ, Hosking CS. Manifestations of milk allergy in infancy: clinical and immunologic findings. *J Pediatr*. 1986;109:270–276
- Bishop JM, Hill DJ, Hosking CS. Natural history of cow milk allergy: clinical outcome. *J Pediatr*. 1990;116:862–867
- Hill DJ, Firer MA, Ball G, Hosking CS. Natural history of cows' milk allergy in children: immunological outcome over 2 years. *Clin Exp Allergy*. 1993;23:124–131
- Host A, Jacobsen HP, Halken S, Holmenlund D. The natural history of cow's milk protein allergy/intolerance. *Eur J Clin Nutr*. 1995;49(suppl 1):S13–S18
- James JM, Sampson HA. Immunologic changes associated with the development of tolerance in children with cow milk allergy. *J Pediatr*. 1992;121:371–377
- Chatchatee P, Jarvinen K-M, Bardina L, Beyer K, Sampson HA. Identification of IgE- and IgG-binding epitopes on α_{s1} -casein: differences in patients with persistent and transient cow's milk allergy. *J Allergy Clin Immunol*. 2001;107:379–383
- Chatchatee P, Jarvinen K-M, Bardina L, Vila L, Beyer K, Sampson HA. Identification of IgE- and IgG-binding epitopes on β - and κ -casein in cow's milk allergic patients. *Clin Exp Allergy*. 2001;31:1256–1262
- Ford RPK, Taylor B. Natural history of egg hypersensitivity. *Arch Dis Child*. 1982;57:649–652
- Bock SA, Atkins FM. The natural history of peanut allergy. *J Allergy Clin Immunol*. 1989;83:900–904
- Hourihane JO, Roberts SA, Warner JO. Resolution of peanut allergy: case-control study. *BMJ*. 1998;316:1271–1275
- Spergel JM, Beausoleil JL, Pawlowski NA. Resolution of childhood peanut allergy. *Ann Allergy Asthma Immunol*. 2000;85:473–476
- Skolnick HS, Conover-Walker MK, Barnes-Koerner C, Sampson HA, Burks W, Wood RA. The natural history of peanut allergy. *J Allergy Clin Immunol*. 2001;107:367–374
- Sampson HA, Ho DG. Relationship between food specific IgE concentrations and the risk of positive food challenges in children and adolescent. *J Allergy Clin Immunol*. 1997;100:444–451
- Vander Leek TK, Liu AH, Stefanski K, Blacker B, Bock SA. The natural history of peanut allergy in young children and its association with serum peanut-specific IgE. *J Pediatr*. 2000;137:749–755
- Hill DJ, Heine RG, Cameron DJ, Francis DE, Bines JE. The natural history of intolerance to soy and extensively hydrolyzed formula in infants with multiple food protein intolerance. *J Pediatr*. 1999;135:118–121
- Daul CB, Morgan JE, Lehrer SB. The natural history of shrimp-specific immunity. *J Allergy Clin Immunol*. 1990;86:88–93
- Pastorello EA, Stocchi L, Pravettoni V, et al. Role of elimination diet in adults with food allergy. *J Allergy Clin Immunol*. 1989;84:475–483

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