

Managing Younger Siblings of Food Allergic Children



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KEYWORDS

• Food allergy • Sibling • Children

KEY POINTS

- Current guidelines state that there is insufficient evidence to recommend testing siblings of food allergic children before introduction of potential allergic foods, but the topic remains controversial.
- The prevalence of any clinically reactive food allergy among siblings of food allergic children is noted to be around 13.6%.
- Among siblings of children with food allergy, the rate of sensitization has been shown to be approximately 50%.
- Risk factors, clinical history, and indications for screening must be carefully balanced with the potential for further sensitization, appropriate follow-up, and economic as well as psychosocial impact.
- These measures have implications for nutrition and overall health, home and social interactions, and quality of life.

INTRODUCTION

Food allergies and food-related adverse events have steadily increased in the United States and worldwide. Food avoidance remains one of the mainstays of preventative

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treatment for food allergies. As such, parents of food allergic children strive to maintain a home, school, and social environment that is free of the specified allergen to try to prevent a life-threatening reaction. Consequentially, a common apprehension for families is the likelihood of siblings developing a similar life-threatening food allergy. Current guidelines state that there is insufficient evidence to recommend testing siblings of food allergic children before introduction of potential allergic foods, but the topic continues to remain controversial. Risk factors, clinical history, and indications for screening must be carefully balanced with the potential for further sensitization, appropriate follow-up, and economic as well as psychosocial impact. These measures have implications for nutrition and overall health, home and social interactions, and quality of life.

EPIDEMIOLOGY

The prevalence of food allergies in the population is important to consider when assessing risk, as it informs the growing public health burden and the predictive value of testing. Food allergy affects at least 7.6% of US children (about 1 in 12), with nearly 42% of those children reporting severe, potentially life-threatening allergic reactions and 40% indicating multiple food allergies.¹ Temporal trends in food allergies have been difficult to interpret given the complexity in means of diagnosis.² Many studies have relied primarily on self-report although some have included more stringent algorithms, specifically with a double-blind placebo-controlled food challenge. The most common food allergens in the United States that account for most of the food allergic reactions include egg, milk, peanut, tree nuts, wheat, fish, shellfish, and soy.³

Most of the studies investigating siblings of food allergic children have focused primarily on peanut allergy alone, reporting an increased risk of peanut allergy in siblings of peanut allergic children.⁴⁻⁶ A recent large cross-sectional study found that the prevalence of any clinically reactive food allergy among siblings of food allergic children was around 13.6% (or about 1 in 8 children).⁷ Among siblings, milk allergy was the most common (5.9%) followed by egg (4.4%) and peanut allergy (3.7%).⁷ Milk allergy in siblings was significantly associated with the index child having both an egg and peanut allergy. Index child refers to the child with a confirmed food allergy to whom the sibling comparison is made. Tree nut allergy in the index child was associated with any food allergy in the sibling, particularly sibling egg allergy and sibling peanut allergy. Peanut allergy in the index child did not increase the risk of peanut allergy in their sibling in this particular study.⁷

Along with the rising prevalence of food allergies are the rates of sensitization or the presence of allergen-specific immunoglobulin E (IgE) to food allergens without evidence of clinical symptoms on exposure to those foods. Among siblings of children with food allergy, the rate of sensitization has been shown to be approximately 50%.⁷⁻⁹ In a study by Gupta and colleagues,⁷ wheat sensitization was the most common among allergens (36.5%), followed by milk sensitization (35.4%) and egg sensitization (35.1%). At the same time, nearly one-third of children were neither sensitized nor had any evidence of a clinical food allergy based on history.⁷

Epidemiologic features of food allergy should be taken into consideration when approaching diagnosis and management of food allergies in siblings of food allergic children, recognizing that self-reported food allergy is more common than clinically diagnosed food allergy and rates of sensitization are several folds higher than clinical reactivity.¹⁰

RISK FACTORS

Food allergy is determined by the interplay of genetic and environmental factors and has a strong association with other atopic diseases. Overall, much remains to be investigated on the risk of food allergy among siblings.

Genetics and Family History

It has been documented that family history is a strong risk factor for food allergy. A large family-based study in the United States found food allergies had significant familial aggregation or the tendency of a disease to cluster in families.¹¹ This association was significant between food allergic children and their mother as well as their siblings. This study also estimated heritability of the most common food-specific IgE levels, suggesting a range of 0.15 to 0.35.¹¹ Heritability is a measure that estimates the influence of genetic versus environmental factors on a disease where values closer to one indicate variability in a trait comes from genetic differences.¹¹ In a small twin study, the concordance rate of peanut allergy among monozygotic twins was much higher than that among dizygotic twins (64.3% vs 6.8%).¹²

Several genome-wide association studies also support a genetic risk for food allergy. A few studies have noted an association between the HLA-DQB1 gene and peanut allergy.^{13,14} However, other studies examining the possible relationship between HLA class II alleles and peanut allergy showed no difference between patients with peanut allergy and siblings who are peanut tolerant.^{15,16} Similarly, the c11orf30/EMSY locus¹⁷ and SERPINB gene cluster¹⁸ have been identified as genetic risk factors for food allergy. Loss-of-function mutations in the filaggrin gene, which encodes a protein important in the skin's barrier function, have also been found to be a risk factor for IgE-mediated food allergy, independent of atopic dermatitis.^{18,19} These genes, however, have not been studied in the context of familial aggregation of food allergies. Moreover, the rate of incidence of food allergies may be rising more quickly than can be accounted for by changes predominantly in the genome sequence.²⁰

Environmental Factors

The likelihood of food allergies amongst siblings is additionally guided by shared environmental and lifestyle factors. It is unknown, however, if environmental exposures are more likely to affect those genetically at risk than those without a family history.

Timing of introduction of potentially allergic foods may be a modifiable risk factor for food allergy, although the direct impact among siblings is unclear. Early introduction of potentially allergic foods seems to be associated with a decreased risk in developing food allergy, causing a shift in current consensus guidelines.^{10,21,22} More recent literature has shown that delayed oral introduction of foods, such as peanuts, may in fact increase the likelihood of peanut allergy.^{22,23} Siblings born after a child was diagnosed with a peanut allergy have been shown to be more likely to never have been exposed to peanuts.^{9,24} This may have been influenced by prior recommendations to defer introduction of allergenic foods, although parental anxiety may also contribute based on the older sibling's food allergy history. A large population-based cohort study found that the initial risk of egg allergy in the sibling of a food allergic child was no longer present after controlling for the timing of introduction of egg.²⁵ The increased risk of egg allergy in the sibling thus was likely related to delayed introduction, in contrast to peanut allergy that may be more guided by genetics, as predicted by heritability estimations.^{11,12,25}

Studies have looked at urban and rural lifestyles,^{26,27} the presence of pets,²⁸ and family size and the presence of siblings^{29,30} among other associations as predisposing versus protective factors in the development of food allergies. More recent investigation has focused on the role of the microbiome in modifying risk for food allergies, as early childhood seems to be critical for the colonization of the gut by diverse microbiota necessary for oral tolerance.³¹ Dietary factors including breastfeeding, probiotics, and vitamin D have additionally been studied.²⁰ Although literature currently

suggests a greater impact on food sensitization than food allergy, environmentally associated evolving patterns and its impact on immune dysregulation continue to be investigated.³² The relationship of environmental exposures amongst siblings of food allergic children is yet to be well defined.

Association with Other Atopic Conditions

Family history of atopy and the presence of atopic dermatitis are strongly correlated with the development of food sensitization and confirmed food allergy.³ Having one family member with atopy affects the likelihood of a child having a food allergy, with this risk increasing nearly 2-fold with 2 or more family members.²⁵ With adjustment for parental atopy and other environmental factors, a history of asthma and eczema was found to be significantly associated with an increased risk for food allergy among siblings.⁷ A large population-based study found that in the absence of parental allergic disease, the risk of food allergy was almost doubled among children with atopic siblings.²⁵ A sibling history of both asthma and allergic rhinitis may predict child egg allergy in particular.²⁵

APPROACH TO FOOD ALLERGY TESTING

Evaluation of food allergy begins with a detailed history to identify potential culprit foods and to establish a temporal relationship with acute IgE-mediated symptoms. The low positive predictive value of self-reported symptoms³³ and frequent lack of definitive physical examination findings necessitates additional diagnostic tools.^{10,34} Specific IgE (sIgE) testing, which includes skin prick testing (SPT), serum tests, or both, and oral food challenges (OFC) are used to aid in the diagnosis of a food allergy. Testing is traditionally limited only to possible allergens, as a positive sIgE test in the absence of a suggestive clinical history is not sufficient for the diagnosis of a food allergy.

In this light, the proposed evaluation of food allergy in siblings of food allergic patients deviates from the conventional approach. Siblings of food allergic patients frequently present for evaluation of food allergies before exposure to the food of concern. The use of SPT or serum tests in the evaluation of these patients is controversial as the absence of a clinical history of a reaction renders interpretation of these results problematic. Positive sIgE tests may reflect sensitization rather than true food allergy and would necessitate further testing with OFC or risk potential inappropriate diagnosis of food allergy. Furthermore, although threshold values have been developed for several allergenic foods to guide clinicians in their interpretation of these results, the question of whether these same cutoffs can be applied in patients without a history of prior exposure remains less clear.

Skin prick testing, a safe and effective method of detecting sIgE antibodies, has low specificity when applied to food.^{10,35} Increasing wheal size is associated with greater clinical relevance of the tested allergen and can be used to predict outcomes of oral food challenges in certain foods.^{10,36–39} The positive predictive value of varying wheal sizes reported in other studies depends on the several factors, including the population and food being tested.^{10,35} In one pediatric study, for instance, a mean wheal size of 8 mm or greater on peanut SPT had a 95% positive predictive value of positive peanut food challenge.⁴⁰ In another study, a wheal size of at least 13 mm was thought to be necessary for diagnosis of food allergy in pediatric patients without prior peanut exposure.⁹ Without standardized thresholds for interpretation of SPT results, especially in a population without a history of exposure, SPT should not be used.

Serum-specific IgE testing is another useful tool in the diagnosis of food allergy but similarly requires the context of medical history. Identification of sIgE alone, without a clinical history of reactivity, suggests sensitization to the allergen but not diagnostic of food allergy.¹⁰ Although predictive values for several foods have been established,⁴¹ these values vary based on population, age, and interval since last exposure to allergen, amongst other factors.¹⁰

Oral food challenge (OFC) can be done in several different ways, including open (or unmasked), single-blinded, double-blinded, and with or without placebo.⁴² Double-blind placebo-controlled food challenge is the gold standard for diagnosis of food allergy. All of these procedures are time and labor intensive, which can limit their use.

CURRENT GUIDELINES

In 2010, the National Institute for Allergy and Infectious Disease (NIAID) sponsored expert panel guidelines for food allergy recommended against routine food allergy testing in high-risk children before introduction of allergenic foods such as milk, egg, and peanut.³ High risk, in this guideline, was defined as a child with a “preexisting severe allergic disease and/or a family history of food allergy.”³ The guidelines did suggest that food allergy evaluation in some populations, such as a sibling with peanut allergy, could be appropriate but argued against routine sIgE.³

In 2014, a food allergy practice parameter was released jointly by the AAAAI, ACAAI, and JCAAI. It recommended that in high-risk children, sIgE testing for highly allergenic foods, such as milk, egg, and peanut, could be considered before introduction.¹⁰ High risk in this guideline was defined as the presence of early severe atopic disease or a sibling or parent with peanut allergy.¹⁰

In 2017, the NIAID added their peanut allergy prevention guidelines to recommend that caregivers of siblings of peanut allergic children have an informed discussion with their providers regarding the overall benefit versus risk of peanut introduction.

CONSIDERATIONS FOR ROUTINE SCREENING

One reason that routine screening of siblings of food allergic children has been widely debated stems from several studies of siblings of peanut allergic patients. These studies found an increased rate of peanut allergy in siblings of peanut allergic children, ranging from 7% to 8.5%,^{4,6,9,12,25} when compared with the rate of peanut allergy in the general population, estimated to be between 1.4% and 3.0%.⁶ Another study demonstrated that the risk of an IgE-mediated reaction to peanuts in siblings of peanut allergic children was 5.2%, with 5 of the 8 reactions presenting as anaphylaxis.⁶ It is likely that the specific inclusion of siblings with peanut allergy as a risk factor for food allergy in the 2014 practice parameter update comes from consideration of these studies.

Parental anxiety about food introduction following an allergic reaction in another child may be another reason that families seek food allergy testing. Ninety three percent of parents in one study reported that their first child's food allergy affected the introduction of foods to younger siblings, with 54% delaying certain foods and 64% of parents avoiding introduction of certain foods.⁴³ A significant percentage of parents (82%) reported anxiety when introducing foods to the younger child.⁴³ Interestingly, 82% of parents in another study reported that they would not follow clinician advice for at-home introduction without testing.⁶ A proportion of these parents may hesitate to introduce certain foods due to the difficulty of safely feeding an allergenic food to one child without also exposing their allergic sibling. In these families,

providing teaching about methods to safely introduce to one sibling may be necessary to facilitate home introduction. Given the risks that delayed food introduction may have on the development of food allergy,²² discussion of screening tests before home introduction versus in-office supervised introduction may be warranted. However, physicians should note that a proportion of parents would still choose not to introduce certain foods at home despite negative testing. As shown by Begin and colleagues,⁶ 15% of parents did not introduce peanut into their child's diet and 34% did not regularly introduce (less than monthly consumption) peanut despite negative peanut food allergy evaluation.

Children with other food allergy risk factors, in addition to a sibling with food allergy, should be referred to a specialist for evaluation of food allergies. The decision to undergo testing before certain food introduction can then be made on an individual basis after frank discussion between the provider and family about the risks and benefits of screening.

CONSIDERATIONS AGAINST ROUTINE SCREENING

In addition to the poor predictive value of sIgE testing,^{3,7} several other concerns argue against routine screening of siblings of food allergic patients. Foremost against routine screening is the high rate of asymptomatic food sensitization without true allergy, which has been estimated to range from 30% to 50% in the general population.^{4,8,44,45} One study found that 22% of children with positive SPT to peanuts were sensitized but not allergic and were able to consume peanuts without difficulty.⁴ Gupta and colleagues⁷ showed that 53% of siblings of food allergic children (or 1 out of every 2 tested) were sensitized but not clinically food allergic. Comparatively, only 13.6% of siblings in this study had a true food allergy.⁷

With such high rates of asymptomatic sensitization, many children may be misdiagnosed with food allergy and recommended inappropriate food avoidance.⁷ Some physicians or providers may incorrectly interpret positive sIgE testing as diagnostic of food allergy and fail to refer these children to allergy specialists for additional evaluation and confirmatory testing, instead opting to advise continued avoidance of tested foods. Similarly, some parents may come to assume that positive testing confirms food allergy and decline to seek or complete further testing. For some children, if sIgE testing results in values greater than certain cutoff levels, they may be deemed allergic and may never be offered the opportunity to undergo an OFC, despite the fact that some percentage may be found to tolerate the food in question.⁴⁶ Indeed, 3.4% of cases of peanut allergy have been estimated to result from overdiagnosis by SPT screening.⁴⁶

The finding of positive sIgE testing warrants further assessment to confirm or refute the diagnosis of food allergy, often done through an oral food challenge.⁶ However, OFCs are frequently delayed, with one study demonstrating that 54% of OFCs were postponed by greater than 12 months after sIgE levels became less than 2kUA/L, a value associated with a high likelihood of passing an oral challenge.⁴⁷ In that study, the average time to OFC was 35.5 months in the delayed group and more than 4 months in the nondelayed group.⁴⁷

A multitude of explanations may be given for deferring OFCs, both from the family/caregiver and from the clinician. Potential reasons may include lack of resources (time, staff, space, training), poor reimbursement, and concern for a potential reaction.^{47,48} For foods without well-defined cutoff levels or component-resolved diagnostics to guide probability of oral tolerance, persistently positive sIgE test results may also delay OFCs. Age of the child may also be a cause of delay as some providers or caregivers may perceive that the child will not cooperate with an OFC or may not be able to

express the development of symptoms.^{42,47} Several studies, including LEAP²² and HealthNuts⁴⁹ have demonstrated that OFC in young children is both feasible and safe. For others, the presence of positive sIgE testing may cause many families to defer evaluation with OFC due to concern for development of reaction and instead proceed with avoidance of those selected foods.⁷ This apprehension is particularly pervasive in families who already have a food allergic child.

Regardless of reason, any unnecessary delay in food introduction may potentially increase the risk of true food allergy development of the avoided food, as has recently been shown by the protective effect of early introduction of peanuts.²²

ECONOMIC IMPACT

Screening siblings of food allergic children has significant implications for economic cost and burden. Although there is no study that has directly calculated the cost of implementation of routine screening of siblings of food allergic children, studies have been completed to evaluate the cost of food allergy and screening before early peanut introduction.

Shaker and colleagues⁴⁶ examined the cost and outcomes of 2 different approaches to early peanut introduction. They compared a no-screening approach to early peanut introduction against screening peanut skin testing and in-office peanut introduction in high-risk infants. Not only did the no-screening approach demonstrate superior clinical outcomes in terms of the number of peanut allergy cases prevented but it also demonstrated significant economic benefits. Compared with the no-screening approach, the cost to prevent one peanut-allergic reaction in the high-risk cohort was \$20,393 using SPT or \$71,020 using sIgE. In their cost calculations, they found that screening the 16% of the infant population with early onset eczema and/or egg allergy in the United States (approximately 641,522 infants) before peanut introduction would levy an additional cost of \$654 million.

Recent US Census records suggest that there are currently approximately 73.8 million children in the United States.⁵⁰ Approximately 1.0% to 2.1% of the pediatric population is composed of younger siblings of peanut allergic children.^{6,9} The implementation of routine screening of these approximately 730,000 to 1.5 million siblings of peanut allergic children, which does not account for the larger population of siblings of any food allergic child, would render a substantial financial burden.

Furthermore, the cost of the consequences of screening cannot be neglected. As discussed earlier, screening may identify a large number of patients with asymptomatic sensitization and result in misdiagnosis of food allergy. The annual medical cost of food allergy has been estimated at \$4184 per year per child.⁵¹ Although patient care and outcomes remain the priority, the economic impact of managing siblings of food allergic patients must also be considered.

EFFECT ON NUTRITIONAL INTAKE AND GROWTH

Health considerations should be emphasized when deciding on an approach to siblings of food allergic children. Food restriction may occur due to family avoidance of the food allergic child's allergens or due to presumed diagnosis or misdiagnosis of food allergy in the sibling. However, limiting dietary intake can have a direct impact on the essential nutrients a child receives and thereby his/her growth and development. For instance, milk avoidance can reduce daily required intake of calcium and vitamin D, potentially affecting bone mineral status as well as motor development.⁵² Wheat, which provides complex carbohydrates, is one of the primary sources of energy for the brain.⁵³ Milk, egg, and soy are important sources of protein and fat, which fuel energy and growth.⁵³

Growth serves as a strong surrogate marker for assessing adequate overall energy and protein intake in children. Indeed, children with 2 or more food allergies are often smaller, by weight and particularly by height, for their age.^{54,55} In addition, Kwashiorkor, a nutritional disorder due to severe protein malnutrition, has been reported in children in the United States on allergen elimination diets.⁵⁶ It is therefore important to address the unintended health impacts that may occur due to restriction of foods for siblings of food allergic children where there is not a clinical need. In addition to children with food allergies, siblings avoiding certain foods for any reason should receive an annual nutrition assessment to incorporate alternative nutrient-dense foods into the diet and prevent growth impairment or inadequate nutritional intake.⁵⁵

PSYCHOSOCIAL IMPACT

Quality of life for the family is an important consideration when approaching management of siblings of food allergic children. Food allergy has been associated with negative psychosocial impact and poorer quality of life for children with food allergy and their families. As such, when managing siblings of food allergic children, extrapolating a food allergy for the younger child may have psychosocial repercussions that can hinder emotional and mental well-being. For instance, children may experience teasing or isolation in social settings because of their presumed food allergy. The stress surrounding the navigation of food avoidance or social interactions can progress to states of anxiety or depression.^{57–59}

Fear of adverse events and anxiety about eating is central to concerns surrounding food allergies and may be more acutely perceived by parents than the child.^{60,61} Food allergy has a significant effect on daily family life such as a meal preparation and family social activities.⁶² Many parents may prefer minimizing the risk and anxiety of possible exposure by avoiding certain activities all together and creating a consistent environment in the home, which could consequentially affect siblings of food allergic children.⁶² In addition to anxiety, time and financial constraints may also dictate meal preparation and thus siblings may end up adopting similar dietary patterns as the food allergic child. The fear of a potential reaction and the disruption due to measures taken to avoid allergen exposure have been shown to be factors associated with a lower quality of life, rather than the actual clinical reactivity experienced by food intake.⁶³

More literature is emerging that investigates the role of parental anxiety after having a previous child with an allergy and how that influences the decision to introduce potentially allergenic foods.⁹ A study of peanut introduction in younger siblings of peanut allergic children examined levels of anxiety related to peanut introduction.⁶ Parents were more likely to introduce at home after negative testing and had increased apprehension to do so without any testing. It is unclear that the fear is based on actual risk but rather seems to be more likely influenced by the negative experiences with the older sibling's allergy.⁶ For patients found to be peanut tolerant who were followed-up after a year, the main reported reason for not introducing the tolerated food, even at low frequency, was difficulty managing risk of cross-contamination or contact with the older sibling.⁶ Of note, for a significant portion of patients who reintroduced peanut at home, there was no cited accidental contact with the allergic sibling.⁶ Some strategies suggested for introduction of foods to the younger sibling that the older child was allergic to, designating a space in the house for consumption, dedicating a time in the week when the older child was absent, and eating only outside the household at restaurants or at other family members' homes.

Ultimately, psychosocial concerns remain an integral part of food allergy management and anticipatory guidance. Physicians should remain alert as well about families' hesitations and be willing to offer more guidance and support to this effect.

SUMMARY

Although the proportion of siblings who are sensitized to a food without clinical reactivity is high in comparison to those with a true food allergy, there is still a known increased risk amongst siblings of children with food allergies that has led to much apprehension and controversy about management. The appropriateness of testing and further steps for management of sensitization in the absence of history of clinical reactivity should be discussed with parents. These siblings are likely to be mislabeled as food allergic when they are in fact tolerant to the food.⁷ This has implications for children down the road, including increased risk of developing allergy due to avoidance, potential for growth and development restrictions, and a negative impact on quality of life.

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