

Should Younger Siblings of Peanut Allergic Children Be Screened for Peanut Allergy?



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The role of screening younger siblings of peanut allergic children with allergy testing before peanut introduction is controversial. Although certain guidelines note some value in screening this population, it is not a direct indication in the recent National Institute of Allergy and Infectious Diseases guideline. Some studies suggest that siblings of peanut allergic children are at increased risk of peanut allergy, whereas others note that delayed ingestion or mislabeling of allergy in these children may be the main factors accounting for this increased risk. The low risk of severe reaction with first ingestion and risks of pre-emptive testing must be balanced against data suggesting that families are reluctant to introduce peanut in siblings without testing. The goal of this article is to critically appraise the debated issues in this topic, providing a practical approach to this common clinical dilemma. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:414-8)

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The role of screening younger siblings of peanut allergic children with allergy testing before introducing them to peanut is an ongoing controversy. The 2010 National Institute of Allergy and Infectious Diseases (NIAID)-sponsored Expert Panel concluded that “there may be some value in food allergy

evaluations ...for a select group of patients with certain risk factors such as having a sibling with peanut allergy.”¹ A 2014 food allergy practice parameter concluded: “For children at high risk, such as children with early development of severe atopic disease or children with a sibling/parent with peanut allergy, sIgE testing can be considered before introduction of certain foods.”² Certainly having a sibling with peanut allergy “may complicate decision making,” as stated in the 2013 Canadian Pediatric Society position statement on allergy prevention,³ and may lead to reluctance to introduce peanut as noted in the 2013 American Academy of Allergy, Asthma and Immunology position statement on prevention of allergic diseases.⁴ The 2017 NIAID expert panel guideline on the prevention of peanut allergy does not list sibling peanut allergy as an indication for pre-emptive testing, although it does acknowledge a role for discussion with a caregiver before introduction in this circumstance.⁵

There are many possible reasons for pre-emptive peanut allergy screening, including increased genetic susceptibility, and discomfort with home introduction in the absence of testing. However, these arguments for testing need to be balanced against a risk that testing may lead to false-positive results and delayed ingestion, inadvertently increasing the risk of peanut allergy.

To date, there has not been a prospective study on this subject, nor a paper specifically dedicated to reviewing this common clinical dilemma. Therefore, the goal of this article is to focus on whether siblings of peanut allergic children should be allergy tested to peanut before introduction.

ARE SIBLINGS OF PEANUT ALLERGIC CHILDREN AT INCREASED RISK OF PEANUT ALLERGY?

One argument in favor of screening siblings of peanut allergic children is the possibility that they are at genetically inherent increased risk of peanut allergy. This notion is supported by 3 observational studies that identified an increased risk of peanut allergy in siblings of peanut allergic children. A nationwide questionnaire of 622 subjects with peanut allergy found a 6.9% prevalence of self-reported peanut allergy in their siblings, which was significantly higher than the rate among parents, aunts, and uncles, or the general population ($P < .001$).⁶ A survey of 58 twin pairs, at least one of whom had peanut allergy, established a pairwise concordance of 64.3% among monozygotic twin pairs, and 6.8% among dizygotic pairs, with an estimated peanut allergy heritability of 81.6% (95% confidence interval [CI], 41.6% to 99.7%).⁷ A birth cohort noted an increased risk of peanut allergy in siblings of peanut allergic children based on survey data of 560 Canadian households (odds ratio [OR] 6.72; 95% CI, 2.04-22.12).⁸ However, a significant limitation of these studies was that peanut allergy was defined predominantly based on self-report, and oral challenges were not routinely performed in any of these studies (Table 1).

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Abbreviations used

CI- Confidence interval

EAT- Enquiring About Tolerance

LEAP- Learning Early About Peanut

NIAID- National Institute of Allergy and Infectious Diseases

OR- Odds ratio

sIgE- Serum-specific IgE

SPT- Skin prick test

A genetic risk for peanut allergy has also been supported by several genome-wide association studies. One study of 311 children with peanut allergy and 226 controls identified an association between 2 allelic groups of the human leukocyte antigen-DQB1 gene and peanut allergy.¹² A recent genome-wide association study and meta-analysis of North American, Australian, and European populations identified the *c11orf30* (*EMSY*) locus as a genetic risk factor for peanut allergy.¹³

However, a large cohort study of 2834 children in Chicago has called into question the notion of an increased risk of peanut allergy in siblings of peanut allergic children.⁹ Gupta et al⁹ examined the risk of food allergy (defined as clinical reactivity and sensitization) among siblings of food allergic children. The most common allergies in siblings were milk (5.9%) followed by egg (4.4%) and then peanut (3.7%). Milk allergy in siblings was significantly associated with egg allergy ($P < .01$) and peanut allergy ($P < .05$) in the index child, and tree nut allergy in the index child was significantly associated with egg allergy ($P < .01$) and peanut allergy ($P < .01$) in siblings. Peanut allergy in the index child did not significantly increase the risk of peanut allergy in siblings nor did peanut allergy in siblings significantly increase the risk of peanut allergy in the index child. Of index children with peanut allergy, 4.9% of siblings were peanut allergic, which was not statistically different from peanut allergy in the siblings of index children with milk, egg, or any food allergy. A key finding was that sensitization without reactivity was common among young siblings, leading the authors to conclude that screening siblings without a history of clinical reactivity appears to be unjustified.

In addition, both delayed ingestion and mislabeling of peanut allergy have been noted in siblings of peanut allergic children, which may be factors explaining an increased risk. This is supported by a study of 932 families within the Canadian Peanut Allergy Registry noting that whereas 8.7% (95% CI, 8.7% to 13.0%) of siblings in a questionnaire were reported as peanut allergic, 42.5% of these siblings had no history of an allergic reaction to peanut.¹⁰ If the siblings were born after a child with peanut allergy, they were more likely to have never been exposed to peanut (OR 6.2; 95% CI, 4.1-9.4) and/or to be labeled as peanut allergic without confirmatory testing or supportive clinical history (OR 12.7; 95% CI, 1.3-120.7). In addition, Begin et al¹¹ conducted a study of 154 peanut naive siblings of peanut allergic children, noting that although overall 5.2% were peanut allergic (based on double-blinded skin testing followed by parent-led introduction), this risk varied significantly based on age of the child. Peanut allergic siblings were significantly older at first ingestion compared with those who did not react (mean 4.0 vs 1.9 years; $P = .04$), further supporting the notion that siblings may be at risk due to delayed ingestion. As a result, waiting for screening may further delay peanut ingestion, and could theoretically increase risk in these siblings.

It is noteworthy that rates of peanut allergy in siblings of peanut allergic children are still lower than rates in other high-risk atopic populations, such as those with severe eczema or egg allergy. HealthNuts, a population based cross-sectional study in Australia, identified that among 5276 infants, 11.4% (95% CI, 3.8-24.6) of children with early eczema or egg allergy had peanut allergy on oral food challenge despite negative peanut skin prick test (SPT, 1-2 mm).¹⁴ In addition, 14% of infants in HealthNuts classified as "high risk" (defined as either egg allergy or early onset <6 months of moderate/severe eczema) were allergic to peanut, higher than the level of risk identified in any studies of younger siblings to date. In the Learning Early About Peanut (LEAP) study of 640 children with either severe eczema or egg allergy, 17.2% were allergic to peanut with avoidance until 5 years of age.¹⁵

Therefore, although there may be some genetic susceptibility in young siblings of peanut allergic children, increased risk may largely be due to delayed ingestion. Studies have established that other risk factors, such as egg allergy and/or severe eczema, place infants at much risk than having a sibling with peanut allergy, and should likely remain the focus of screening policies at this time, in keeping with the NIAID expert panel peanut allergy prevention guideline.

WILL FAMILIES OF PEANUT ALLERGIC CHILDREN INTRODUCE PEANUT AT HOME WITHOUT PRE-EMPTIVE TESTING, AND WHAT IS THE RISK IF THEY DO?

Another argument in favor of pre-emptive testing of siblings is that some families of peanut allergic children may not be comfortable introducing peanut to the sibling without evaluation. This was demonstrated in Begin et al's study,¹¹ which evaluated parental acceptability of various peanut introduction scenarios (at home without testing, at home after negative or positive testing, supervised introduction) in siblings of peanut allergic children. There was a significant difference in median anxiety scores between all the responses ($P < .05$), with higher anxiety levels noted for home introduction without testing (median 8.4 on the 10-point Likert scale) compared with both home introduction after negative testing (median 4.3, $P < .0001$) and supervised introduction without testing (median 3.8, $P < .0001$). Levels of anxiety about home introduction were significantly higher than in families without allergic children (median 4.0 on the Likert scale). In addition, when families of peanut allergic children were asked what they would do if their physician recommended at-home peanut introduction without pre-emptive evaluation in another sibling, 82% (95% CI, 75% to 88%) stated that they would continue to avoid peanut, and 53% (95% CI, 45% to 63%) stated that they would seek a second opinion. It is possible that the high degree of anxiety with introducing peanut at home was due to the time at which the study was performed (February 2013 to February 2015), which was before the LEAP study and the subsequent 2017 NIAID prevention guidelines. Also, it is unknown if the use of this unvalidated Likert scale to assess anxiety in families of infants with severe eczema and/or egg allergy would have given similar results.

Indeed, concern about peanut introduction may be endemic in families of allergic children in general, and not specific to families with a peanut allergic child. A cross-sectional online

TABLE I. Studies on the risk of peanut allergy in younger siblings of children with peanut allergy

Author	Study design	Atopic characteristics of young siblings	Definition of PA	Outcome
Hourihane et al ⁶	Nationwide survey of 622 adults and children with reported, suspected, or known PA	Eczema 28.2%, asthma 23.0%, rhinitis 24.8%. In a subset of local children's siblings: eczema 23%, asthma 18%, rhinitis 23%	Self-report; subset of 50 local children (mean age, 5 y) and their first-degree relatives evaluated with SPT ± OFC	↑ Risk of PA in siblings of children with PA (prevalence 7%)
Sicherer et al ⁷	Interview by validated questionnaire of 58 twin pairs, at least one of whom had PA	N/A	Self or parental report (median age 5 y) including convincing reaction history; SPT/sIgE not required but reported in 74%	↑ Risk of PA in monozygotic pairs (estimated heritability 81.6% [95% CI, 41.6% to 99.7%])
Liem et al ⁸	Survey of 560 households in Canada who were part of a nationwide cohort of both peanut allergic children and nonallergic controls	N/A although index children part of a case-control cohort at high risk of asthma	Parental report including report of assessment by board-certified allergist and of carrying epinephrine autoinjector; allergists of siblings were contacted but not a requirement for diagnosis	↑ Risk of PA in siblings of children with PA (OR 6.72 [95% CI, 2.04-22.12])
Gupta et al ⁹	Nested cohort of 2834 children in Chicago Family Cohort Food Allergy Study (1120 children with food allergy and at least 1 biological sibling)	Rates not reported; ↑ risk of food allergy among siblings with history of eczema ($P < .01$) and asthma ($P < .01$)	Sensitization (SPT or sIgE) and the reported history of typical symptoms of an allergic reaction to peanut	4.9% of siblings had PA; PA in the index child did not significantly increase the risk of PA in sibling. High rates (53%) of sensitization with no history of clinical reactivity
Lavine et al ¹⁰	Questionnaire sent to 932 families within the Canadian Peanut Allergy Registry	N/A	Parental report of reaction to peanut, results of clinical testing to peanut, and diagnosis of PA by a physician	PA in 8.7% (95% CI, 7.0-10.7); 42.5% of those had no history of a clinical reaction. If born after a sibling with PA, more likely to never have been exposed to peanut (OR 6.2 [95% CI, 4.1-9.4])
Begin et al ¹¹	Prospective double-blind assessment of 154 peanut naive younger siblings of peanut allergic children	Eczema 22%, asthma 1%, rhinitis 1%, other food allergy 2%	Reaction on medically supervised parent-led introduction to peanut; double-blind SPT, and sIgE, done before introduction but results did not impact introduction	↑ Risk of PA in siblings of children with PA (5.2% [95% CI, 2% to 10%]); those who reacted significantly older (median 4.0 vs 1.9 y; $P = .04$)

CI, Confidence interval; N/A, not assessed; OFC, oral food challenge; OR, odds ratio; PA, peanut allergy; sIgE, serum-specific IgE; SPT, skin prick test.

survey of 644 Canadian parents and caregivers who had a food allergic child found that if a family chose to delay introduction of allergenic foods to a younger sibling, peanut was the most common food that was delayed or avoided (90.7%) despite only 48.8% of the index children having peanut allergy.¹⁶ In addition, the HealthNuts study noted that in 5276 infants, it was the infant's atopic history (early onset eczema or milk/egg reactivity), not family history of food allergy, that led to delayed peanut introduction ($P < .001$ and $P = .32$, respectively).¹⁴

Despite potential caregiver concern about peanut introduction in siblings, the risk of severe or fatal anaphylaxis with first exposure to peanut is exceedingly low. A retrospective study of all anaphylaxis fatalities in children in the UK and Ireland over a 10-year period noted 8 anaphylaxis fatalities overall (risk 1 in 800,000 per year), the majority of which were to milk (4/8 fatalities).¹⁷ There were no peanut fatalities in children below 13 years of age, and no near-fatal reactions caused by peanut. A 2015 review of anaphylaxis literature over a 10-year period described anaphylaxis fatality as a "rare and extraordinary event" with an incidence of 0.12 to 1.06 deaths per million person-years.¹⁸ In general, mortality is associated with older age,¹⁸ causes other than food allergy (such as medication or stinging insect allergy),¹⁸ and, in the case of food allergy, almost always occurs in those with a previously diagnosed food allergy, rather than on a first exposure.^{19,20} Perhaps the most important statistic is that there are no documented fatalities on first exposure to peanut documented in the literature.

Several studies have shown at-home peanut introduction to be very safe. The Enquiring About Tolerance (EAT) study elegantly demonstrated the safety of peanut introduction in a large cohort of 1303 infants who were randomized to early (3 months) or standard (6 months) introduction of 6 allergenic foods including peanut.²¹ Although these were general population infants, there was a high rate of atopy within the EAT study population—24.4% of these infants had eczema and 91.9% had parental report of atopy. A significant finding of this study was that even very early peanut introduction was safe—there were no cases of anaphylaxis with the introduction of allergenic foods at home in the early-introduction group. The HealthNuts study had a similar experience. There were no life-threatening events in 5276 infants, irrespective of atopic status, who were introduced to peanut in the first year of life, or in 150 peanut-allergic children during in-hospital oral challenges.¹⁴

Because there is significant evidence that the risk of a severe reaction on first exposure to peanut is exceedingly low and no evidence of fatality on first exposure to peanut in young children, families could be first counseled that peanut introduction is safe without pre-emptive testing rather than the approach of promoting blanket screening of young siblings. However, a patient-centered approach is still required despite this, as evidence suggests that many families with peanut allergic children will not introduce peanut to other siblings without a pre-emptive evaluation.

WHAT ARE THE HARMS OF PRE-EMPTIVE PEANUT EVALUATION BEFORE INTRODUCTION?

A concerning consequence of screening siblings of peanut allergic children is that it may lead to overdiagnosis of peanut allergy. In a recent editorial, Turner and Campbell²² discussed the limitations of peanut screening tests—noting its lack of

specificity, as many children who generate peanut specific IgE are clinically tolerant. Although Begin et al's study¹¹ found a low false-positive peanut SPT rate (3.8%), other contrasting studies have suggested that screening (either SPT or serum-specific IgE [sIgE]) carries a significant rate of clinically irrelevant sensitization in children, especially if they are atopic. For example, Gupta et al's study⁹ of 2834 Chicago children highlighted a very high rate of clinically irrelevant sensitization (53%) among siblings of peanut allergic children. In the LEAP study, 22% of infants with severe eczema and/or egg allergy had a positive sIgE to peanut, of whom only 2% had positive oral challenge results.^{15,23} In fact, it has been estimated that <40% of children with positive SPTs or sIgEs are food allergic on oral food challenge.²⁴ It is unclear why Begin's rate of clinically irrelevant sensitization was so much lower than that reported in many other studies, although it may relate to a higher median age of the young siblings (23 months) or perhaps predominantly mild eczema, as eczema severity was not quantified in the study.

A screening policy for all young siblings would also be difficult to implement, as there may be issues with lack of access to a specialist, long wait lists to see a specialist, or lack of medical insurance to cover that cost. This has not been studied in siblings of peanut allergic children in particular, but has been examined for infants with severe eczema or egg allergy, for whom pre-emptive peanut evaluation is recommended based on the NIAID guideline.⁵ With this recommendation, concerns have been raised about logistics and resource availability, such as access to care.^{14,22,23,25,26} For example, there are currently only 5440 board-certified allergists in the United States and approximately 260 in Canada.²⁶ Koplin et al¹⁴ noted that pre-emptive screening "would pose major cost and logistic challenges that need to be carefully considered." In addition, the concern about a "screening creep" has been highlighted, where "parental pressures and perhaps physician over-cautiousness" may result in testing to foods other than peanut.²²

In conclusion, testing siblings of peanut allergic children carries the risk of overdiagnosis of peanut allergy, as well as delayed peanut introduction due to the lack of resources available for this screening. Delayed peanut introduction in young siblings due to a blanket screening policy could ironically negate the benefits of early introduction identified by the LEAP study. However, this must be carefully balanced against the risk that if a family is concerned about peanut introduction, they may delay if no pre-emptive testing is offered as well.

CONCLUSIONS

A younger sibling with peanut allergy is not an absolute indication for pre-emptive screening of peanut allergy based on current guidelines including the NIAID guideline. A large part of the increased risk for a younger sibling is likely due to delayed introduction, rather than an inherent genetic risk; therefore, early peanut introduction appears to be of essence. Instead of a screening policy, education should be the first priority to prevent delayed introduction. Perhaps education in 2018 about the safety of home introduction is an easier concept for parents to grasp, with recent events including the publication of the LEAP study in 2015 as well as the NIAID guidelines in 2017. If a family is comfortable, peanut should be given at home in an age-appropriate manner at around 6 months of life, with assurance that a serious or life-threatening reaction is exceedingly rare

and that there is no evidence of fatality on first exposure. Focus should remain on the infant's atopic status as the key determinant of screening, with egg allergy and/or severe eczema as the main criteria for pre-emptive testing, to avoiding overtesting infants or medicalizing feeding.

However, some individualization is still required. If a family is not comfortable with at-home peanut introduction, as studies suggest is often the case for many at-risk categories, health care provider evaluation followed by in-office oral food challenge should be considered, resource-permitting. Other factors, such as household capabilities, may also be considered if a family feels that they cannot safely keep peanut away from the older allergic sibling in the home. Possible suggestions include offering peanut outside of the home to the young sibling, assigning designated eating areas for the young sibling to consume peanut, care to not share eating utensils, and cleaning of surfaces with soap and hot water, which removes peanut protein. The development of educational tools, such as handouts that outline how peanut can be introduced to younger siblings, may be helpful as well.

Further studies are required to accurately determine the relative risk of genetics versus environment in young siblings of peanut allergic children. For example, one could compare peanut introduction in siblings of peanut allergic children with controls (no family history of peanut allergy) at around 6 months of age using oral food challenges as the outcome, comparing rate of reactivity while adjusting for infant atopic history and the presence of genetic markers. In addition, a registry of severe reactions with peanut introduction would provide information about unexpected or particularly severe reactions.

Until such studies are performed, families should be encouraged to introduce younger siblings to peanut at around 6 months of age at home if they are comfortable doing so through proper education, bearing in mind that some pre-emptive evaluation will likely still be required for those who are hesitant despite education.

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