Rostrum

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

Elissa M. Abrams, MD[a,b], Edmond S. Chan, MD[b], and Scott H. Sicherer, MD[c] *Winnipeg, MB, Canada; Vancouver, BC, Canada; and New York, NY*

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;■:■-■)**

Key words: *Peanut allergy; Allergy prevention; Food allergy*

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 I).

[a]Department of Pediatrics, Section of Allergy and Clinical Immunology, University of Manitoba, Winnipeg, Manitoba, Canada
[b]Department of Pediatrics, Division of Allergy and Immunology, University of British Columbia, Vancouver, British Columbia, Canada
[c]Department of Pediatrics, Division of Allergy and Immunology, Icahn School of Medicine at Mount Sinai, New York, NY

No funding was received for this work.
Conflicts of interest: E. M. Abrams has received moderator fees and an unrestricted educational grant from Novartis. E. S. Chan has received research support from DBV Technologies; is a shareholder in Aimmune Therapeutics; and is an expert panel and coordinating committee member of the National Institute of Allergy and Infectious Diseases (NIAID)-sponsored Guidelines for Peanut Allergy Prevention. S. H. Sicherer receives grant support to his institution from NIH (NIAID) and HAL allergy; receives royalties from UpToDate and Johns Hopkins University Press; receives an honorarium from the American Academy of Allergy, Asthma, and Immunology as Associate Editor of *JACI In Practice*; and served on the expert panel and as a coordinating committee member of the NIAID-sponsored Guidelines for Peanut Allergy Prevention.
Received for publication November 27, 2017; revised January 3, 2018; accepted for publication January 10, 2018.
Available online ■■

Corresponding author: Elissa M. Abrams, MD, Department of Pediatrics, Section of Allergy and Clinical Immunology, University of Manitoba, FE125-685 William Avenue, Winnipeg, MB, R3E0Z2, Canada. E-mail: elissa.abrams@gmail.com.

2213-2198

https://doi.org/10.1016/j.jaip.2018.01.002

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 al[9] 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 al[11] 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