Identifying infants at high risk of peanut allergy: The Learning Early About Peanut Allergy (LEAP) screening study

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Background: Peanut allergy (PA) is rare in countries in which peanuts are introduced early into infants' diets. Learning Early About Peanut Allergy (LEAP) is an interventional study aiming to assess whether PA can be prevented by oral tolerance induction.

Objective: We sought to characterize a population screened for the risk of PA.

Methods: Subjects screened for the LEAP interventional trial comprise the LEAP screening study cohort. Infants were aged 4 to 10 months and passed a prescreening questionnaire.

Results: This analysis includes 834 infants (mean age, 7.8 months). They were split into the following: group I, patients with mild eczema and no egg allergy (n = 118); group II, patients with severe eczema, egg allergy, or both but 0-mm peanut skin prick test (SPT) wheal responses (n = 542); group III, patients with severe eczema, egg allergy, or both and 1- to 4-mm peanut wheal responses (n = 98); and group IV, patients with greater than 4-mm peanut wheal responses (n = 76). Unexpectedly, many (17%) in group II had peanut-specific IgE sensitization (≥0.35 kU/L); 56% of group III were similarly sensitized. In contrast, none of the patients in group I and 91% of those in group IV had peanut-specific IgE sensitization. Sensitization on skin testing to peanut (SPT response of 1-4 mm vs 0 mm) was associated with egg allergy and severe eczema (odds ratio [OR], 2.31 [95% CI, 1.39-3.86] and 2.47 [95% CI, 1.14-5.34], respectively). Similar associations were observed with specific IgE sensitization. Black race was associated with a significantly higher risk of peanut-specific IgE sensitization (OR, 5.30 [95% CI, 2.85-9.86]). Paradoxically, for a given specific IgE level, black race was protective against cutaneous sensitization (OR, 0.15 [95% CI, 0.04-0.61]).

Conclusion: Egg allergy, severe eczema, or both appear to be useful criteria for identifying high-risk infants with an intermediate level of peanut sensitization for entry into a PA prevention study. The relationship between specific IgE level and SPT sensitization needs to be considered within the context of race. (J Allergy Clin Immunol 2013;131:135-43.)

Key words: *Peanut sensitization, peanut allergy, allergy risk factors, eczema, egg allergy, patient recruitment, allergy prevention, LEAP study*

The prevalence of peanut allergy (PA) among children in the United Kingdom, North America, and Australia has doubled in 10 years and is approximately 1.8%, 1.4%, and 3.0% respectively.[1-7] PA is a common cause of anaphylaxis and is infrequently outgrown.[8-12] The onset of IgE sensitization to peanut usually occurs during infancy, with symptomatic PA typically presenting during early childhood.[13-15]

Studies eliminating food allergens during pregnancy, lactation, and infancy have consistently failed to prevent IgE-mediated food allergy.[16] There are no recommendations aimed at the prevention of PA through avoidance or exposure to peanut during pregnancy, breast-feeding, and infancy.[17-19] The Learning Early About Peanut Allergy (LEAP) study[20] is a randomized controlled trial in infants that aims to determine which is the best strategy for the prevention of PA: introduction of peanut into the diet of young infants or complete avoidance. An intervention needs to be applied to a high-risk population before subjects become

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Abbreviations used
LEAP: Learning Early About Peanut Allergy
OR: Odds ratio
PA: Peanut allergy
PP: Per-protocol
SPT: Skin prick test

clinically allergic to be an effective prevention strategy. The LEAP study sought to enroll infants at high risk for the development of PA. A review of the literature suggested that eczema severity, early onset of eczema, and frequent use of topical corticosteroids might be useful high-risk factors for the development of PA.[14,21] There are also data showing an association between egg allergy and PA.[22] We therefore decided to use severe eczema, egg allergy, or both as inclusion criteria for the LEAP study. We anticipated that infants with a skin prick test (SPT) wheal diameter to peanut of 0 to 4 mm would not yet have established PA; children with wheal diameters of greater than 4 mm were considered likely to have PA and therefore excluded from the prevention study.[23-27]

In this article we prospectively assess whether severe eczema and egg allergy are effective inclusion criteria for the identification of infants at high risk for peanut sensitization but without established PA.

METHODS

Study design

The LEAP screening study is a single-center, prospective, observational study that includes infants who underwent screening for an interventional trial termed the LEAP study (see the Methods section in this article's Online Repository at www.jacionline.org), which investigated the prevention of PA in high-risk children. Recruitment was targeted to families with young infants with eczema, egg allergy, or both. In this article the term *eczema* is identical to the term *atopic dermatitis*. Recruitment focused on (1) child health professionals, such as dermatologists, allergists, and specialist nurses; (2) a study flyer posted to parents of young infants in the United Kingdom; and (3) other avenues, such as written and electronic media and word of mouth. Interested families were asked to make contact with the study team either through an external call center or directly. Infants underwent screening for the LEAP study if the family agreed to consider participation in the study and passed a prescreening questionnaire addressing previous allergy and eczema history.

Demographics

Information about prior eczema and other allergies was gathered through interviews. Information about race was based on families' self-report. In the United Kingdom, where the study took place, subjects who identify themselves as black are predominantly Afro-Caribbean or African. Thus the black population in the current study is not identical to the American black population. Those who identify themselves as Asian are predominantly from the Indian subcontinent.

Severe eczema

Eczema was self-defined by participants' parents by a questionnaire. Severe eczema was defined as one of the following: (1) frequent need for treatment with topical corticosteroids or calcineurin inhibitors, (2) parental description of "a very bad rash in joints and creases" or "a very bad itchy, dry, oozing, or crusted rash," or (3) a severe SCORAD grade (≥40) by a clinician before or at the time of screening.

Egg allergy

Egg allergy was defined on the basis of either (1) an SPT-induced wheal diameter of 6 mm or greater with raw hen's egg white and no history of previous egg tolerance or (2) an SPT-induced wheal diameter of 3 mm or greater with pasteurized hen's egg white with a history of an allergic reaction to egg.[28]

SPTs and specific IgE measurements

SPTs to ingested allergens, including raw hen's egg white (Red Lion salmonella-free egg), pasteurized hen's egg white, peanut, cow's milk, sesame, and soya (all other SPTs sourced from ALK-Abelló, Hørsholm, Denmark), were undertaken at the baseline assessment. The lyophilized peanut extract contains 20 mg of peanut protein per vial; analysis by means of Western blotting confirmed the presence of Ara h 1, Ara h 2, and Ara h 3. By using a standardized lancet (ALK-Abelló), the skin on the forearm was pricked through a drop of the extract. Peanut SPTs were undertaken in duplicate, with the widest diameter of the wheals at 15 minutes recorded and averaged.[24] A saline control was not subtracted. Cutaneous sensitization for peanut was generally defined as an SPT response of greater than 0 mm, except in Fig E4 and Tables E2 and E3 in this article's Online Repository, in which it was defined as an SPT response of 3 mm or greater.

At baseline, specific IgE assays (Thermo Fisher Scientific, Uppsala, Sweden) were undertaken for peanut, hen's egg white, cow's milk, sesame, brazil nut, hazel nut, cashew, almond, and walnut. Three cutoffs for specific IgE levels were used. Detectable specific IgE levels were defined as greater than 0.01 kU/L. An intermediate cutoff of 0.1 kU/L or greater was used in some analyses. Sensitization by specific IgE was defined as a result of 0.35 kU/L or greater.

Sample size

The number of infants screened was based on the need to enroll 640 participants in the LEAP study. Additional details are given in the Methods section in this article's Online Repository.

Statistical analysis

We categorized all infants who were screened into groups of increasing atopy. Group I, with "mild eczema and no egg allergy," did not meet LEAP study inclusion criteria. Group II, with "severe eczema and/or egg allergy but no reaction on SPT to peanut," is the LEAP study negative SPT response stratum. Group III, with "severe eczema and/or egg allergy and a 1-4 mm peanut wheal," is the LEAP study positive SPT response stratum. Group IV have peanut wheal responses of greater than 4 mm. Groups I to IV comprise the LEAP screening study cohort. Each group was described in terms of its demographics and clinical features. Trends were examined with 2-sided Cochran-Armitage trend tests. Spearman correlation coefficients were used to assess the association between SPT responses to different foods and between specific IgE results to different foods. Participants were split into 3 severity groups based on SCORAD scores (mild, <15; moderate, 15-40; and severe, >40)[29] at screening to explore the relationship between eczema severity and sensitization. A similar methodology was followed for the peanut SPT-induced wheal diameter groups. Finally, baseline factors associated with sensitization to peanut were analyzed by using univariate and multivariate logistic regression models.

Ethical considerations

Ethical approval for the study was provided by the NRES Committee London – Fulham, formerly West London REC2 Ethics Committee (REC Reference 04/Q0403/13). Informed consent was obtained from the parents of all participants.

RESULTS

Demographics of screened subjects

Infants were recruited for the LEAP study from November 2006 to May 2009. A total of 2829 potential participants