Managing Nut Allergy: A Remaining Clinical Challenge

Philippe A. Eigenmann, MD[a], Gideon Lack, FRCPCH[b], Angel Mazon, MD[c], Antonio Nieto, MD[c], Diab Haddad, MRCPH[d], Helen A. Brough, FRCPCH[b], and Jean-Christoph Caubet, MD[a] *Geneva, Switzerland; London and Chertsey, United Kingdom; and Valencia, Spain*

Peanut and tree nut allergies have become a public health problem over the last 2 decades. The diagnostic procedure relies on a suggestive history, as well as on evidence of sensitization (skin prick testing and/or specific IgE blood testing), followed in selected cases by a food challenge. Standard IgE tests may be positive to more than 1 nut, due to cross-reactivity (allergens common to several nuts) or cosensitivity (frequently associated positive test results without cross-reactivity). Thus, many patients with a peanut or a tree nut allergy avoid all nuts, relying on positive test results without clinical evidence of reactivity. In addition, coexisting pollen sensitivity may add to diagnostic uncertainty due to potential cross-reactivity between pollens and nuts. In this article, we discuss challenges in diagnosis and clinical management of peanut and tree nut allergy related to cross-reactivity and cosensitization, as well as the avoidance of nuts tested positive to reduce the risk of reactions by cross-contamination. Studies to provide more accurate characterization of genuine clinically relevant cross-reactivity or cosensitivity to multiple nuts are needed. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:296-300)

Key words: *Peanut allergy; Tree nut allergy; IgE testing; Cross-reactivity*

In the first half of the 20th century, milk, cereal grains, and hen's egg were reported as the most common food allergens.[1] Reactions to nuts were then mostly anecdotal, such as in the report from 1931 by Vaughan in which peanut allergy is reported as a cross-reacting legume eliciting urticaria in a young female patient.[2] Systemic allergic reactions to tree nuts (commonly included in the tree nut family are almond, Brazil nut, cashew nut, hazelnut, walnut, pecan, pistachio, and macadamia nut) but also mostly to peanut have been increasingly reported only in the last quarter of the 20th century, leading to the concept of the "peanut allergy epidemic."[3-5]

To a large part, peanut and tree nut allergy has gained public attention due to the severity of the reactions. These foods have been identified as the main culprits of fatal or near-fatal reactions in 2 successive reports published in the United States in the late 1980s and early 1990s.[6,7] Strikingly, most of these children had a reaction to more than 1 nut. This led to the general recommendation in peanut- or tree nut—allergic patients to avoid all types of nuts, often regardless of positive or negative test results. In addition, preventive avoidance of nuts never eaten was advised although clear scientific evidence was lacking.[8] Overall, safety has been advocated also to avoid reactions by cross-contaminating nuts. These recommendations have largely contributed to the number of children avoiding all nuts in the community. Evidence is lacking as to whether extended or targeted avoidance influences the quality of life of these patients or their risk of future reactions.

[a]Pediatric Allergy Unit, University Hospitals of Geneva and University of Geneva, Geneva, Switzerland
[b]King's College London, Medical Research Council and Asthma UK Centre in Allergic Mechanisms of Asthma, Division of Asthma, Allergy and Lung Biology, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom
[c]Children's Hospital La Fe, Pediatric Pulmonology and Allergy Unit, Instituto de Investigacion La Fe, Valencia, Spain
[d]St Peter's Hospital, Chertsey, United Kingdom

Conflicts of interest: P. A. Eigenmann has consultancy arrangements with Microtest DX, DBV technologies, Nestlé, Gesellschaft zur Förderung der dermatologischen Forschung und Fortbildung e.V., Danone, and Novartis; is employed by the University Hospitals of Geneva; has provided expert testimony for the European Food Safety Authority (EFSA); has received 1 or more grants from or has 1 or more grants pending with the Swiss National Science Foundation, the Ulrich Muller Gierock Foundation, and Leti; has received 1 or more payments for lecturing from or is on the speakers' bureau for ThermoFisher and Sodilac; has received royalties from UpToDate and Elsevier; owns stock/stock options in DBV Technologies; and has received 1 or more payments for travel/accommodations/meeting expenses from the European Academy of Allergy and Clinical Immunology (EAACI). G. Lack has been supported by 1 or more grants from the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), Food Allergy & Research Education (FARE; contribution to NIAID contract/grant), Medical Research Council (MRC) & Asthma UK Centre (contribution to KCL Division of Asthma, Allergy & Lung Biology of which Paediatric Allergy is a part), the UK Department of Health through National Institute for Health Research (NIHR) (Biomedical Research Centre Award to Guy's & St. Thomas' National Health Service [NHS] Foundation Trust), the National Peanut Board (support for Paediatric Clinical Trials Unit), and the UK Food Standards Agency and has received 1 or more grants from or has 1 or more grants pending with the MRC (contribution to KCL Division of Asthma, Allergy & Lung Biology of which Paediatric Allergy is a part). A. Nieto is a board member for Novartis; has consultancy arrangements with Novartis, Diater, and Meda; and has received 1 or more payments for lecturing from or is on the speakers' bureau for Novartis, Meda, Uriach, Leti, and Diater. H. A. Brough has consultancy arrangements with MEAD Johnson Nutrition and Nutricia; has received a FARE Charity grant and has received 1 or more grants from or has 1 or more grants pending with the Immune Tolerance Network and the NIH; has received 1 or more payments for lecturing from or is on the speakers' bureau for Meda Pharmaceuticals, Thermo Scientific, and Nutricia; and has received royalties from Wiley Blackwell Ltd. J.-C. Caubet has received support for travel from Thermofisher and has received 1 or more grants from or has 1 or more grants pending with the Muller Foundation. The rest of the authors declare that they have no relevant conflicts of interest.
Received for publication January 14, 2016; revised July 16, 2016; accepted for publication August 22, 2016.
Available online October 25, 2016.
Corresponding author: Philippe A. Eigenmann, MD, Pediatric Allergy Unit, University Hospitals of Geneva, 6 rue Willy-Donze, 1211 Geneva 14, Switzerland. E-mail: Philippe.Eigenmann@hcuge.ch.
2213-2198

http://dx.doi.org/10.1016/j.jaip.2016.08.014

Abbreviations used
BAT- basophil activation test
OFC- oral food challenge

In this rostrum, we discuss peanut and tree nut allergy, and identify knowledge gaps to be addressed in future research for improvement of diagnosis and management of nut-allergic patients.

PEANUT AND TREE NUT ALLERGIES ARE COMMON, BUT UNEVENLY GEOGRAPHICALLY DISTRIBUTED

The prevalence of food allergy largely varies between studies but can be estimated to affect up to 10% of the population.[9] Epidemiological data commonly show that peanut allergy is affecting up to 3% of the population, with the highest numbers found mostly in the United Kingdom, Australia, and North America. A North American random telephone survey conducted by Sicherer et al[5] reported among 188 households the most common nut allergies to be as follows: peanuts (53%), walnut (22%), cashew (16%), pecan (26%), almond (25%), pistachio and Brazil nut (10%), hazelnut and macadamia nut (9%), and pine nut (6%). Overall, the estimated prevalence of peanut and/or tree nut allergies was 1.4%.[5] In a Canadian random telephone survey, the estimated prevalence was similar, with 1.4% for tree nut allergy and 0.93% for peanut allergy.[10] In the United Kingdom, a birth cohort study from the Isle of Wight estimated the prevalence of peanut allergy at 1.3%.[3] In an Australian population-based study with challenge proven allergy, Osborne et al[11] found peanut sensitization in 8.9% and sesame in 2.5% of 12-month-old infants, and peanut and sesame allergy in 3.0% and 0.8%, respectively. Peanut was also clearly identified as the second most common food eliciting allergy (in 24%) after egg (in 25%) in South African children with atopic dermatitis.[12]

Large efforts to define the food allergy epidemiology in Europe have been recently undertaken by the EuroPrevall research consortium with cross-sectional population-based studies in children and adolescents, as well as in adults. First analysis showed that hazelnut was overall the most common sensitizing nut in the adult EuroPrevall cohort at 9.3% (lowest, Iceland 1.3%; highest, Switzerland 17.8%), followed by walnut at 3.0% (lowest, Iceland 0.1%; highest, Spain 7.7%) and peanut at 2.7% (lowest, Iceland 0.5%; highest, Spain 7.2%).[13] Although for many years peanut allergy was found mostly in North America, the United Kingdom, and Australia, EuroPrevall data have shown that peanut has now also become a prevalent cause of food sensitization in many European countries. A recent meta analysis showed that in Continental Europe, the most prevalent tree nut allergy was hazelnut, with large geographical variations (depending on the studies between 17% and 100% of all tree nut allergies).[14] Unlike Continental Europe, walnut and cashew allergies are most common in North America, whereas Brazil nut and walnut allergies are among the most frequent nut allergies in the United Kingdom.[15,16]

However, in most studies, the estimates of the prevalence of peanut and tree nut allergies have been based on sensitization, and/or a convincing history, and rarely on a standardized food challenge, explaining the large heterogeneity of epidemiological data.

We have seen that peanut allergy is unevenly distributed, and one of the possible explanations for the low prevalence of peanut allergy in some countries such as Israel may be early introduction of peanuts into the infants' diet.[17] Nevertheless, other regions of the world such as Siberia also have low rates of peanut and nut allergy (<1%), albeit in the absence of early peanut introduction.[18] These observations suggest that the timing of introduction of a food is important, but it is only one factor among many influencing the development of food allergy.

POSITIVE TEST RESULTS TO NUTS MAY NOT BE CLINICALLY RELEVANT

Thirty-five percent of patients allergic to peanuts or tree nuts may present with multiple nut allergy as suggested in 1998 by Sicherer et al.[19] This questionnaire survey followed by examination and serologic testing of the patients showed that 92% had positive specific IgE test results and 37% had a reaction to more than 1 nut. Similar numbers were seen in a case-control study from the United Kingdom, in which one-third of the patients had experienced allergy to more than 1 nut. Most common allergies were to peanut, followed by Brazil nut, almond, and hazelnut.[20] Clark and Ewan[21] also showed that the number of nuts a child ate increased with age (23% eating more than 1 nut at 2 years, 73% by 10 years), and they postulated that this was leading to higher rates of multisensitization (19% at 2 years, 86% at 5-14 years) and multiallergy (2% at 2 years to 47% at 14 years).[21] In a retrospective study by Brough et al,[22] more than half of children previously tested for nut allergy were found to develop new nut sensitization over a 2- to 4-year follow-up and more than one-third developed a new nut allergy.

Allergy to certain well-defined combinations of nuts may be due to the presence of similar or closely related epitopes. Such closely related epitopes are more common in phylogenetically closely related nuts. This has been observed for pistachio and cashew nuts (extensive cross-reactivity between rPis v 3 and rAna o 1)[23] and for pecan and walnuts (between rCar i 4 and rJug r 4).[24] Nuts sharing proteins from similar families, for example, storage proteins such as vicillins, are also highly cross-reactive.[25]

The cross-reactivity due to shared storage protein family such as the vicillins may explain why nonrelated nuts such as tree nuts and peanuts can serologically and clinically cross-react. This raises the question whether nut-allergic patients are at risk of allergic reactions to seeds such as sesame, or even to pine nuts, because these may contain storage proteins similar to those of nuts. A survey among members of the UK anaphylaxis campaign asked about coexisting allergy to sesame and peanut. Eighty-four percent of the responders reported sesame seed allergy as well as tree nut and/or peanut allergy.[26]

In most cases, standard diagnostic workup does not allow differentiation between clinical cross-reactivity and coallergy, versus serological cross-reactivity and cosensitization in a given patient (Figure 1).

POLLEN SENSITIVITY IS A COMMON CAUSE OF CROSS-REACTIVITY IN NUT ALLERGY

Patients allergic to birch pollen show a high rate of cross-reactivity mostly to hazelnuts, but also to various other nuts.[27] These patients suffer from oral allergy syndrome, characterized by symptoms predominantly localized in the oropharynx. Ability to distinguish between patients with oral allergy syndrome and