

Selective nut-eating in peanut or tree nut allergic children—How can molecular allergology help?

The study by Uotila et al raises the interesting discussion of selective nut eating, which is growing in interest. The authors found that in Finland the majority of children with challenge-proven peanut allergy were avoiding tree nuts, spanning from coconut avoidance in 52% of children to pecan nut avoidance in 93% of cases. Brazil nut, pecan and macadamia were the least frequently eaten, whereas sesame was avoided in only 26% of patients; one important aspect regarding these data is the fact that these nuts are not part of the regular diet in Finland. Children with suspected peanut allergy had positive skin prick tests to a range of tree nuts ranging from 37% (Brazil nut) to 76% (pistachio). By assessing molecular allergens (using ISAC microarray for peanut molecular allergens, sesame (Ses e 1), walnut (Jug r 1), Brazil nut (Ber e 1) and single ImmunoCAPs for hazelnut (Cor a 14) and cashew (Ana o 3), the authors were able to decipher that the majority of these positive skin prick tests were due to birch pollen cross-reactivity rather than due to positive IgE against the immunodominant seed storage proteins (where available). Finland is a region where birch pollen is highly prevalent, as in other Scandinavian countries and parts of Northern Europe; thus, birch pollen cross-reactivity would be expected in these regions rather than in regions such as Southern Europe, where sensitisation to lipid transfer proteins (LTPs) is more common.¹ In fact, in Finland, specific IgE to seed storage proteins were positive in only 6% (for both sesame and Brazil nut), 15% (for both walnut and pecan using Jug r 1), 25% (for hazelnut) and 27% (for cashew and pistachio using Ana o 3). Of note, some studies have suggested that the sensitivity of ISAC can be lower compared to skin tests and specific IgE, and this needs to be taken into account when interpreting the results of this method.²

Thus, despite positive skin prick tests, the authors concluded that the majority of children could possibly introduce tree nuts into their diet. The authors proposed that if species-specific components are negative this was sufficient to rule out allergy to these tree nuts. However, they advised that previously avoided tree nuts should be introduced with caution as there may be other allergens not tested thus there was a chance of a potentially severe allergic reaction. Although diagnostic food challenges were not performed to the tree nuts in this study, previous studies suggest a higher probability of a negative challenge with negative IgE to seed storage proteins.³ However, due to pollen-food syndrome, localised symptoms may develop. It is important to note that these findings apply to a birch pollen endemic region. Indeed, in the Mediterranean region, children with

negative IgE to seed storage proteins can have systemic reactions due to LTP sensitisation, although most LTP-sensitised patients have mild or no symptoms upon ingestion of the incriminated nut. We agree with the authors that if children have positive allergy tests (either skin prick tests or specific IgE) then these nut introductions should be performed in hospital rather than at home. For these cases, based on the results of the specific IgE to component allergens and the clinical history, an oral food challenge (OFC) can be performed as a supervised feed in a low-risk setting⁴ if seed storage proteins are negative (such as an outpatient setting), but if allergy tests are higher, then these are best performed in a day-case setting for a standard OFC. Some allergy centres allow home food introduction if both the blood test and skin prick test are negative, provided there is no history of reaction, clear written instructions are given to patients and they have availability of medication to treat allergic reactions.⁵

Peanut and tree nut allergy often co-exist; however, few studies have used OFCs to determine the challenge proven rate of co-existent allergy. Previously, co-existent peanut and tree nut allergy was reported to be between 20%-59% based on self-reported questionnaires and/or IgE testing (by specific IgE or skin prick testing).⁶⁻⁹ However, these modalities are limited by over-reporting of allergic symptoms, false diagnosis, and positive tests related to cross-reactivity to pollen or cross-reactive carbohydrate determinants; all these factors might result a spuriously higher rate of reported allergy. More recently, the rate of challenge proven co-existent peanut and tree nut allergy was cited as <30%.¹⁰⁻¹² However, these studies were mainly conducted retrospectively,^{10,11} and/or only included a limited number of tree nuts.¹⁰⁻¹² Sesame seed allergy also co-exists with peanut allergy. In 2 studies 58%-84% of children with sesame sensitisation or reported allergy were also sensitised or had reported allergic reactions to peanut;^{13,14} 25% of children with peanut allergy were reported to have sesame seed allergy.¹⁴ Prospective studies are ongoing to investigate the challenge proven rate of co-existent allergy between peanut, tree nut and sesame such as the Pronuts study (<https://clinicaltrials.gov/ct2/show/NCT01744990>) which is a prospective multi-centre study in UK, Geneva and Spain.

In the study by Uotila et al, OFCs were performed in children with suspected peanut allergy, based on either peanut skin prick test ≥ 8 mm or peanut sIgE ≥ 15 kU/L or a weaker sensitisation but life-long avoidance of peanut. OFCs were positive in only 67.6% of challenges, which shows the importance of performing OFCs. Peanut skin prick test ≥ 8 mm and peanut sIgE ≥ 15 kU/L cut-offs have been shown in UK and US populations to have 95% positive predictive value (PPV) for challenge-proven peanut allergy,^{15,16} but 95% PPV have been

higher in the Netherlands and France.^{17,18} In this Finnish population, these allergy test levels may have had a lower predictive value due to birch pollen cross-reactivity. The authors found what has been previously described,¹⁹ that Ara h 2 and 6 are the best in vitro differentiators for a positive peanut challenge (Ara h 6 was in fact a better predictor than Ara h 2). Ara h 8 was slightly higher in the peanut tolerant group than peanut allergic groups and thus the authors said it was not a useful test for the diagnosis of peanut allergy. We would agree with this statement, although this is still useful in evaluating pollen-food syndrome versus primary peanut allergy in selected cases.

In conclusion, management of patients with peanut and/or tree nut allergy is evolving and selective introduction of nuts is gaining momentum. Component allergens are useful to identify patients that might tolerate a given nut and distinguish positive tests due to pollen cross-reactivity versus primary food allergy. An over-restrictive diet impacts quality of life;²⁰ however, introducing selective nuts carries the risk of a potential allergic reaction, and regular ingestion is needed to maintain tolerance, which may not be feasible if the nut is not part of the regular diet. The debate is open and all these aspects need to be taken into account when considering selective nut eating in a child with peanut and/or tree nut allergy.

ORCID

Helen A Brough  <http://orcid.org/0000-0001-7203-0813>

Helen A Brough^{1,2,3} 
Caubet Jean-Christoph⁴

¹Children's Allergy Service, Guys and St Thomas' NHS Trust, London, UK

²Paediatric Allergy Group, Department of Women and Children's Health,
School of Life Course Sciences, London, UK

³Paediatric Allergy Group, School of Immunology & Microbial Sciences,
King's College London, London, UK

⁴Paediatric Allergy Department, Geneva University Hospital, Geneva,
Switzerland

Correspondence

Helen A Brough, Children's Allergy Service, Evelina Children's Hospital,
Guys and St Thomas' NHS Trust, London, UK.
Email: Helen.brough@gstt.nhs.uk

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