

The development and progression of allergy to multiple nuts at different ages

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The aims of this study were to define the development of sensitization and clinical allergy to multiple nut types by age, and to identify associations. This observational cross-sectional study was carried out in a tertiary level allergy clinic. Seven hundred and eighty four nut-allergic children, prospectively enrolled on first attendance with history of a type-1 allergic reaction shortly after definite nut ingestion with evidence of sensitization (presence of nut-specific IgE) by skin prick test (SPT) to peanut, Brazil, almond, hazel and walnut (positive ≥ 3 mm). Details of exposure (tolerance or allergy) to each nut were obtained. The main outcome measures were mono or multisensitization (specific IgE to one or more than one nut type, demonstrated by SPT); mono or multiallergy (clinical allergy to one or more than one nut type). By 2 yr of age at least 19% were multisensitized, and 2% multiallergic. Increasing proportions were exposed to multiple nut types with increasing age (23% at 2 yr to 73% by 10 yr) and greater proportions were multisensitized (19% at 2 yr to 86% at 5–14 yr) and multiallergic (2% at 2 yr to 47% at 14 yr). This study is the first to define the natural history of multiple nut allergies in childhood. New findings are that a large proportion of those aged 0–1 yr with nut allergy are already sensitized (have specific IgE) to multiple nut types, implying *in utero* or early life sensitization; those who present later in childhood are increasingly likely to be sensitized and clinically allergic to multiple nuts. This is related to increased duration of allergy and exposure to multiple nut types with age. Children with nut allergy should avoid all nut types from the onset.

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Peanut allergy is a common clinical problem (1), the prevalence has increased over the past 4 yr (1, 2) and it now affects 1.5% of children (1, 3). It is the commonest cause of fatal and near-fatal food allergic reactions (4–6) and consequently its natural history has been closely studied (7–9). Most peanut-allergic children react to their first apparent ingestion and clinical sensitivity is retained for many years, with a small chance of resolution (7, 8). In studies where no intervention has been specified, further reactions to peanut are common (10). Sensitization (the presence of specific IgE) and clinical allergy to tree nuts is common amongst children with peanut allergy, with 32% of peanut allergic children having sensitization to tree nuts and 21% reporting

clinical allergy (8, 9, 11). Tree nut allergy is long-lasting and can cause severe and fatal reactions (12–14); there is also potential for frequent dietary contamination (15). Despite this, there are few studies of how peanut and tree nut allergies are related in childhood, with which to inform general practitioners, paediatricians or allergists, who all encounter such patients frequently. As a consequence, families are often given inconsistent advice about avoiding nuts other than those to which their children are allergic, clinicians are unsure whether to test for sensitization to the tree nuts in children with peanut allergy and further reactions are common (8). We therefore studied the pattern of sensitization and reported clinical allergy to a wide

range of tree nuts in a large cohort of peanut-allergic children to provide new data on the natural history of sensitization and clinical allergy to multiple nuts in childhood.

Method

This was an observational, cross-sectional study of children attending a single allergy clinic, mostly referred by their general practitioner. Anonymous data were collected prospectively, over a 9-year period, after interview with an allergist from 784 children with a typical history of an acute allergic reaction to a nut and evidence of nut specific IgE by positive skin prick test (SPT) (≥ 3 mm – performed by a specialist allergy nurse). A typical history meant acute onset of one or more of the following features: urticaria, angioedema, pruritus of the oro-pharyngeal mucosa, laryngeal oedema, asthma, abdominal pain and/or vomiting, light headedness, fainting or collapse occurring immediately or soon after ingestion of a food known to contain a nut. History of allergy or tolerance to individual nuts, details of different nut-types ingested and a full allergy history were also obtained. Each child had SPT, using standardized technique and solutions (ALK Abelló, Hoersholm, Denmark) to peanut, Brazil, almond, hazel and walnut (except where limited by age-related factors). This group of peanut/tree nuts was chosen, as it is known to cause the majority (86%) of patients 'worst reactions' (13). Data were analysed using GraphPad Prism (2.0; San Diego, CA, USA); contingency tables were analysed with chi-square test of the null hypothesis; $p < 0.05$ was taken to be significant.

Definitions

Sensitization: the presence of IgE specific to a particular nut type; **mono/multisensitization:** the presence of specific IgE to one/more than one nut type; **clinical allergy:** allergic reaction to a specific nut type characterized by angioedema, urticaria and/or airway and/or cardio-vascular effects; **mono/multiallergy:** history of clinical allergy to one/more than one nut type.

Results

Clinical features

Seven hundred and eighty four peanut or nut-allergic children; median age 5 yr (0.6–15 yr); male: female ratio = 1.3:1; median age at onset is 2 yr. The worst ever reaction in 479 (64%)

children was mild only (cutaneous features), 218 (28%) had a moderately severe reaction (with symptoms of airway narrowing) and 58 (8%) had a reaction with severe dyspnoea and/or collapse. In 29 (3%) details of the worst reaction were not available. About 535 (68%) children had their worst ever reaction to peanut and 93 (12%) to Brazil nut (Table 1). Overall, 636/784 children were sensitized to peanut (81%), 360 to Brazil (46%), 319 to hazelnut (41%), 309 to almond (39%) and 180 to walnut (23%).

The pattern of exposure to multiple nut types in childhood

For children aged less than 2 yr at presentation, 23% (11/48) had knowingly ingested more than one nut type. With increasing age at presentation, a greater proportion had eaten more than one nut type, up to 73% by 10 yr (Fig. 1).

The pattern of sensitization to multiple nuts

Overall, 76% (593/784) were sensitized to more than one nut type. At least 19% (9/47) of infants (<2 yr) were sensitized to multiple nut types. For age-related reasons, an additional 32% (15/47) had only a single SPT so information on multiple sensitization was missing. A proportion

Table 1. Peanut/nut type which caused each subject's worst ever reaction, $n = 784$

	n	%
Peanut	535	68
Brazil nut	93	12
Hazel nut	44	6
Walnut	21	3
Almond	14	2
*Other/mixed	77	9

*Other/mixed includes cashew, pecan, pistachio, sesame and pine nut or where nut content was identified but the individual nut type was not determined.

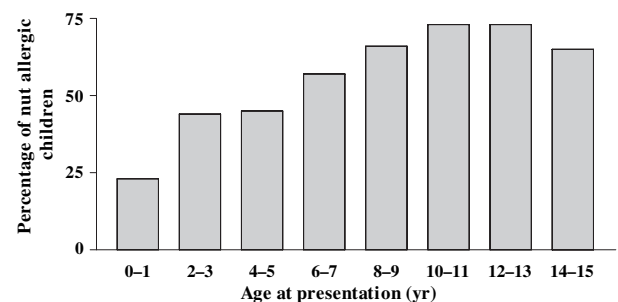


Fig. 1. Percentage exposed to multiple nut types for each age of presentation; $n = 784$. Chi-square test for trend for numbers of subjects: $\chi^2 = 43.9$; $p < 0.0001$.

of these infants will have been multisensitized, so the estimate of 19% of infants being sensitized to multiple nut types must be a minimum.

The proportion of children with multiple sensitizations increased rapidly with age at presentation (Fig. 2), 72% were multisensitized by 4–5 yr of age.

For multisensitized children, the number of nut types they were sensitized to increased with age at presentation. For example, of those presenting less than 2 yr of age 57% were sensitized to two nut types and 22% to more than three. For those who presented aged 12–13 yr, 12% were sensitized to two nut types and 71% were sensitized to more than three ($p < 0.0001$; Fig. 3). Twenty eight per cent of SPT wheals of nut types causing multisensitization were ≥ 8 mm diameter, 72% were 3–7 mm diameter.

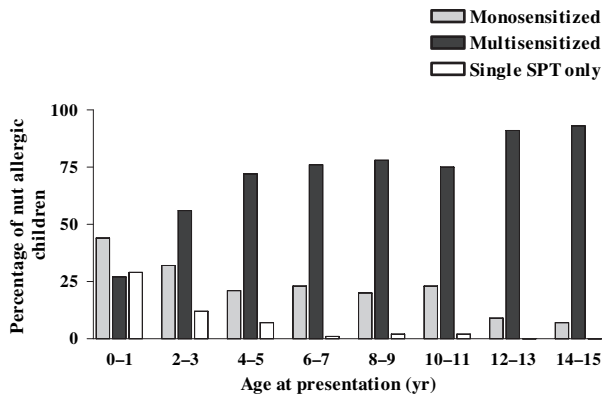


Fig. 2. Percentage sensitized to one nut type only (monosensitized) or multiple nut types (multisensitized) for each age at presentation. In some cases young children had SPT to only a single nut type (single SPT only), so it is not known if they were mono or multisensitized; $n = 784$ (chi-square test for trend, $\chi^2 = 120.2$, $p < 0.0001$).

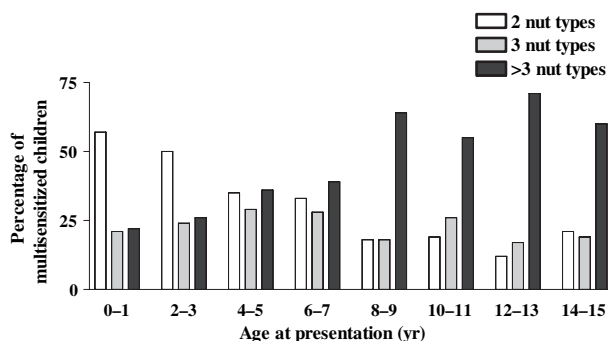


Fig. 3. Percentage of multisensitized children sensitized to either two, three or more than three nut types by age at presentation; $n = 531/784$ (chi-square test, $\chi^2 = 138.2$, $p < 0.0001$).

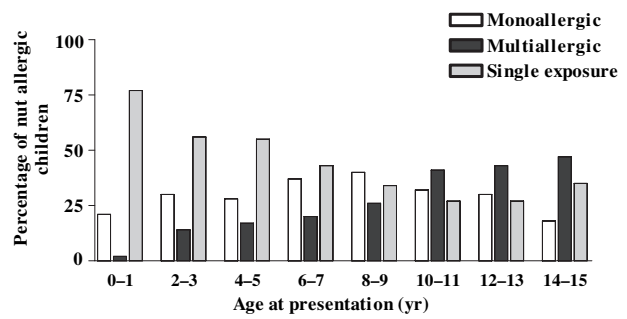


Fig. 4. Percentage with a history of a clinical reaction to one nut type only (monoallergic) or multiple nut types (multiallergic), for each age of presentation. Some children had only ever been exposed to a single nut type by age at presentation (single exposure); $n = 784$ (chi-square test for trend, $\chi^2 = 89.4$, $p < 0.0001$).

The proportion of multiallergic children increases with age

Overall, 22% (175/784) of peanut or nut-allergic children reported clinical reactions to multiple nut types. The proportion of children allergic to more than one nut type was greater with increasing age at presentation (from 2% at 0–2 yr to 47% at 14 yr). The majority of children aged 10–15 yr had multiple nut allergies (Fig. 4). A proportion in each age group had only ever knowingly eaten one nut type so it is not known if these individuals were mono or multiallergic.

Duration of allergy before enrolment

Mean duration of allergy was correlated with increasing age at presentation, with a significant linear trend ($r^2 = 0.98$, $p < 0.0001$). The mean duration of allergy for children who presented at 4–5 yr was 2 yr (95%CI: 1.9–2.2 yr), but for children who presented at 14–15 yr the mean duration was 8.7 yr (95% CI 7.4–10.3 yr).

Overall, 57% (21/37) of children who presented to allergy clinic for the first time at 15 yr of age had been without expert help for more than 10 yr, 76% were multiallergic and 89% multisensitized.

Discussion

New findings are that a substantial proportion of infants who present with peanut/nut allergy are already sensitized (have specific IgE) to more than one type of nut. Children who present later are more likely to be sensitized and clinically allergic to a greater number of nut types. This is related to increased exposure.

Questionnaire studies have suggested that 35–50% of peanut allergic adults and children also report allergy to tree nuts (8, 16). However,

results from such studies may include many non-allergic subjects. About 175/784 (22%) of children in our study had multiple nut allergies, confirmed by careful clinical history and SPT. Other studies found 37% of adults and children allergic to peanuts were also allergic to tree nuts (11) with 53% sensitized to multiple nut types by age 7 yr (9). One study examined serum specific-IgE levels to peanut, hazel and Brazil nut, showing similar patterns of sensitization in infancy and adulthood, but there was no information on clinical allergy (17). The present study is the first to examine, as its primary outcome measure, the association between increasing age at presentation and exposure to multiple nuts, and the development of sensitization and allergy to multiple nuts.

Early life sensitization

Peanut allergy most commonly begins in the second year of life (7) and the majority of reactions (81%) occur on the first known ingestion, implying prior occult sensitization (8). Maternal ingestion of peanuts during pregnancy and breast feeding, use of peanut- or soya-containing formula milk, trace contamination of infant diet and use of arachis- or soya-oil containing eczema creams have all been implicated (9, 18, 19). In 1998 the Committee on toxicity of chemicals in food (COT) advised that if there is a family history of atopy, pregnant women might wish to avoid the consumption of peanuts and peanut products, in an attempt to reduce the impact of occult sensitization (20). No advice on avoidance of tree nuts was introduced, despite the increased availability of tree nut containing products in the diet. We do not have information on whether our cohort had been exposed to this advice or were compliant with it, but we have shown that a high proportion of newly diagnosed predominantly peanut-allergic infants, born after the publication of this advice, are sensitized to multiple nut types (19%). We recognize that our estimate is a *minimum* and the true proportion is likely to be even greater. The majority of families of multisensitized infants (89%; 8/9) can only recall ingestion of a single nut type, again suggesting prior occult sensitization, either to a cross-reacting allergen, or exposure to a novel nut. The early onset of multiple nut sensitization and allergy implies that this takes place either *in utero* or soon after birth. If the COT advice were extended to include avoidance of tree nuts in pregnancy and during breastfeeding the impact would need to be assessed by a longitudinal study.

Development of further sensitization/allergy in older children

For many older children there was a long duration of allergy between the first clinical reaction and presentation to this allergy clinic. As there is no consensus on management, during this period they would have received variable advice on which other nuts they were sensitized to, and which other nuts they should avoid. We have shown that by the time of presentation, the majority of older children had ingested multiple nut types, either accidentally or not, and the majority were sensitized and allergic to multiple nut types. It is possible that those children who reported allergy to multiple nut types had reacted to contamination of the new nut by the original allergen. This is unlikely as in each case multiple clinical allergies were only included in the analysis if matched by multiple sensitizations. Children who presented at a younger age may have either come from more highly motivated families or being born more recently, had been more influenced by the increasing public awareness of nut allergy. Nut avoidance is difficult for families and children. In a survey of nut-allergic subjects not receiving expert advice, 75–92% reported suffering a nut reaction over the previous 2–5 yr (7). In the UK and France, if families and schools are enrolled in a comprehensive management plan (11, 21, 22) between 15% and 30% will have a further reaction. Our data support the advice that children who present with nut allergy should be counselled to avoid all nut types and not just the ones to which they have reacted. Early referral to allergy services ensures the spectrum of sensitization and clinical allergy for each child is clearly defined, together with implementation of a comprehensive management plan, including advice on nut avoidance, an individualized written treatment plan, training in the use of emergency medication and education of parents and teachers (21, 22). Longitudinal studies could examine whether this approach, through careful avoidance, will reduce the progression to multiple nut allergies.

The clinical relevance of multiple sensitizations is not known with certainty. Wheal diameters of 3–7 mm lie in a 'grey area' where approximately half of all patients have clinical allergy, and half do not (13, 23). However, SPT wheal diameter ≥ 8 mm for peanut (≥ 4 mm for 0–1-year old) is 95% predictive of clinical allergy (23). Approximately 28% of positive SPT wheals from multisensitized individuals in this study were ≥ 8 mm diameter (72% were 3–7 mm) suggesting that sensitization would be matched by clinical allergy in a significant number. Nonetheless, it

is important to identify positive SPTs with 3–7 mm wheal diameter to other nuts, as these indicate a 50% chance of clinical allergy to that nut type (13).

It would have been preferable to follow subjects longitudinally but studies of nut allergy resolution show that nut allergy phenotype changes very slowly over many years (24, 25), making this impractical. We did not use the double blind placebo-controlled food challenge (DBPCFC), which causes a small risk of inclusion of non-allergic children. Instead we used a very large sample of patients with a clear-cut history of an allergic reaction after definite nut ingestion assessed by experienced allergists and confirmed by SPT. The latter reduces the likelihood of inclusion of non-nut-allergic patients, and the former reduces the impact of this. This study is the largest series to be published investigating children with nut allergy, including patients with a clear cut history after definite nut ingestion, and confirmed by SPT. This is a commonly used diagnostic method and makes the results from this study widely applicable to many outpatient settings in general practice, paediatrics, respiratory medicine and allergy.

There are currently no disease-modifying therapies available to nut allergy sufferers but many are being developed (19). Until these become available nut-avoidance will continue to underpin management. We have shown that increasing age is related to greater sensitization and clinical allergy to nuts. Longitudinal studies would be of value to confirm whether intervention in pregnancy and early childhood with strict nut avoidance measures will prevent the development of multiple nut allergies.

Acknowledgments

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