

Outcome of mixed nut biscuit challenges in low risk patients who are on tree nut exclusion diet

To the Editor,

Nut allergy has a significant impact on the psychosocial wellbeing and the quality of life of nut allergic children and their families[1]. Currently, many children diagnosed with a peanut or tree nut allergies are advised to avoid all nuts. To maintain these dietary restrictions requires constant vigilance and use of coping mechanisms when eating at home, at restaurants and when traveling abroad[2, 3]. Furthermore the concept of blanket nut avoidance in a selectively peanut allergic child has been challenged[4], and the benefit of early introduction of peanuts amongst children who were at high risk of developing clinical peanut allergy has been recently highlighted[5]. The utility and applicability of positive serological tests to accurately diagnose clinical nut allergy has been examined[6]. Ludman et al recently highlighted the value of an elevated specific IgE (sIgE) level as a predictor of tree nut allergy in sensitised children[7]. We sought to describe the outcome of mixed nut biscuit challenges in a cohort of patients who have predominantly negative or small positive skin prick tests (SPTs), and assess the significance of positive tree nut sIgE in these patients.

Methods

A retrospective clinical audit of all patients 18 years and younger who underwent an open mixed tree nut biscuit challenge over a 12 month period were evaluated at Princess Margaret Hospital (PMH).

All children had either avoided tree nuts as they were peanut allergic and cross reactivity to tree nuts was unknown, had previous sensitisation to tree nuts with no convincing history of clinical reaction, or were avoiding tree nuts due to history of nut allergy in a sibling or other family member. Children had SPTs performed to six tree nuts, namely almond, Brazil nut, cashew, hazelnut, macadamia and walnut, in the outpatient clinic prior to challenge. Only those nuts to which SPT was negative or small positive ($<5\text{mm}$ mean SPT weal diameter) were included in the tree nut biscuit recipe at the discretion of the treating physician.

The SPT size on the day of the challenge was recorded. The SPT was performed on the volar aspect of the forearm using a 1mm lancet (Stallergenes, Paris, France) and commercial tree nut extracts (Alyostal, Stallergenes) with a positive (histamine 10mg/ml) and negative (normal saline) control. The SPT was performed and read as per the published guidelines of the Australasian Society of Clinical Immunology and Allergy[8]. Not all patients were tested to all six nuts (Table 2). The result was read at 15 min and the mean diameter was calculated as an average of the maximum and perpendicular weal diameters.

Tree nut specific IgE was measured using the ImmunoCAP fluorescent-enzyme immunoassay (Phadia, Uppsala, Sweden) within 6 months before the challenge. Results were reported in a range of <0.35 to $>100\text{kU}_A/\text{L}$ and were considered positive if $\geq 0.35\text{kU}_A/\text{L}$.

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Mixed tree nut biscuit challenges

A mixed tree nut biscuit was defined as a biscuit containing 3 or more tree nuts. The nuts to be included in the particular biscuit were selected according to the assessment made by the treating physician. Patient's parents were asked to bake and bring a mixed tree nut biscuit adapted from a previously published mixed nut biscuit recipe [4] but amended to include macadamia, a commonly eaten nut in the local context. The biscuit was administered as a 5-step procedure starting with 1/16, 1/8, 1/4, 1/2 and the remainder of the biscuit given at 15 min intervals. Eight grams of each nut to be challenged was included in the biscuit. No child refused to eat the biscuit demonstrating the palatability and the ease of administration of multiple nuts in a single challenge.

Challenges were conducted in an outpatient setting or in the day procedure ward. Specialised nurses were equipped to manage allergic reactions including life-threatening anaphylaxis. The patients were observed for 2 hours following the completion of the mixed tree nut biscuit challenge and tolerant children were advised to eat the tree nuts contained in the biscuit regularly (at least once per week). Children were classified as tolerant if they completed their challenge without reacting and remained tolerant at a follow up phone call 2-4 weeks post challenge. A positive challenge was defined as objective signs of an IgE mediated reaction (at least three or more non contact urticaria persisting longer than 5 minutes, generalized skin erythema, angioedema, rhinoconjunctivitis, cough, wheeze, stridor, abdominal pain, vomiting and hypotension)[9]. Informed consent for the challenge was obtained from the parents and the institutional ethics committee approved the study.

Statistical methods

Descriptive statistics were given as median and range (min-max) for continuous variables and frequency and percent for categorical variables. Continuous variables included the age of the child at challenge, tree nut mean SPT weal size on the day of the challenge and sIgE results. An exact binomial test was used to compare the observed and the expected frequencies of positive sIgE, with the expected frequency defined as 0.5 regardless of challenge outcome. These analyses were carried out using SPSS version 16.0 (SPSS Inc, Chicago, IL, USA).

Results

Ninety-nine children underwent 99 open mixed nut biscuit challenges of which the majority was conducted in outpatients (60%). Of these 1 challenge did not proceed as the SPTs were deemed too large on the day, 2 were excluded due to incomplete documentation and a further 8 as their biscuit had less than 3 nuts or contained other seeds therefore 88 patients were included in the final analysis. The majority were male (55%) with a median age of 7.6 years (range 1.9-17.5 years). The subjects were atopic with 43.6% with eczema, 34.5% with allergic rhinitis, 33.3% with concomitant asthma and 73.2% reported a history of atopy in the family (Table 1). Forty children were administered a six nut, 27 underwent a five nut, 12 underwent a four nut and 9 underwent a three nut biscuit challenge.

The frequency of the individual tree nuts included in the biscuit and their respective SPT and sIgE is outlined in Table 2. Of children with negative SPT who had sIgE results available, 46.2% (127/275) had positive sIgE for the same nut. Of those, 88% had a sIgE level of <5 kU/L (44% between 0.35-1 kU/L, and 44% between 1-5 kU/L). In children with negative SPT, there was no significant difference in the observed frequency of positive vs negative sIgE results for any nut except Brazil nut.

Three children (3%) had a positive mixed TN biscuit challenge with one equivocal result (subjective symptoms only). There were no cases of anaphylaxis. One child developed facial urticaria after 1/16 of a biscuit. A second child had vomiting, facial erythema and sneezing after ¼ of a biscuit. The third child developed angioedema of the buccal mucosa with erythema of the overlying skin after ¼ of a biscuit containing almond, Brazil and walnut. A fourth child had subjective oral symptoms after 1/16 of a biscuit that were similar to the symptoms induced on previous exposure to peanut to which he has a confirmed allergy; challenge was ceased and he was advised to avoid tree nuts. Walnut was included in the biscuit for each of these patients, and the first, second and fourth children had positive walnut SPT of 5, 6 and 3.5mm respectively. The third child had negative SPT on day of challenge, but 3 months earlier had positive SPT to almond (3mm) with a walnut weal of 2mm.

Discussion

Children diagnosed with a single nut allergy may be advised to avoid all nuts, an approach advocated following observations that an increasing proportion of children initially allergic to a single nut may develop multiple nut allergies with increasing age [10]. This approach of avoidance affords little diagnostic clarity for peanut allergic individuals and their families as to their allergic status with regards tree nuts, and the LEAP study demonstrated the benefit of early introduction of peanuts for children at high risk to reduce their likelihood of developing peanut allergy[5]. Precautionary advisory labeling may contribute to anxiety around food choices[11] and confirming tolerance to selected tree nuts may remove unnecessary dietary restrictions. However, caution must still be exercised regarding cross-contamination (particularly of snack food items[11]) and patients may sensibly adhere to a more restricted diet when travelling or remote from medical attention to minimize risk of inadvertently ingesting a nut to which they are allergic.

Our study demonstrates that a positive tree nut sIgE in the absence of a clinical history of reaction and in the context of a negative or small positive SPT was a poor predictor of tree nut allergy. In a SPT negative patient, if sIgE positivity were a contraindication to challenge 127 of 421 (30.1%) tree nut challenges would not have proceeded. Conversely 95% of children (84/88) were able to reintroduce nuts into their diet and unnecessary food allergy labels removed.

A recent paper suggests a significant increase in the likelihood of a positive challenge in the presence of a maternal history of allergy and positive sIgE, particularly those patients with sIgE >5 kU/L[7]. Only a small number of children in that cohort had SPT performed (34 children) and therefore this variable was excluded from the final analysis. In an allergy practice SPTs are considered routine and inform clinicians in their decision on the need for additional testing. Specific IgE testing is widely available to non-immunologists, including general practitioners and paediatricians, and has potential benefits over SPTs in terms of standardisation and reproducibility. The potential appeal of sIgE measurement to predict likelihood of allergy is therefore understandable, however our findings are consistent with previous literature highlighting the risk of over diagnosis of food allergy due to misinterpretation of food sIgE measurement, leading to unnecessary food elimination diets especially in highly atopic patients[6]. Further it highlights that there is poor agreement between SPT and sIgE to tree nuts and that a negative SPT is a better indicator of tree nut tolerance, as previously established[12].

There are several methodological limitations of this study. Firstly our data set was retrospective and therefore reliant on the documentation of the primary clinician. In addition although our cohort had either a history of peanut sensitization or allergy, those referred for mixed nut biscuit challenge had a relatively low sensitization pattern to tree nuts and are not representative of all patients with severe clinical allergy to peanut. The challenge mixed tree nut biscuit was prepared at the patient's home and not standardized with all tested tree nuts. The protein content challenged did not equal to 3000mg of protein reflective of final threshold dose as per International standards[13], however the amount of each nut included was felt to be an age-appropriate portion consistent with the recommendation of a published expert report on oral food challenge testing[14].

Despite the inherent bias this study demonstrates with careful patient selection in a supervised setting administration of a mixed tree nut biscuit is safe, practical and palatable compared to single nut challenges that are tedious in the young child. Furthermore children should not be excluded from a mixed tree nut biscuit challenge solely on the basis of positive sIgE results.

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Table 1. Patient characteristics

	n/N*	%
Gender		
Males	49/88	55.0
Females	39/88	45.0
Atopic History	63/85	73.2
Eczema	38/86	43.6
Allergic Rhinitis	30/86	34.5
Asthma	28/86	33.3
Peanut allergy or sensitisation		
Previous clinical history	48/79	61.2
Positive SPT	58/81	71.9
Positive sIgE	59/64	92.1

*N = Number of patients for whom relevant information was available from records

Table 2. Summary of results of SPT and sIgE for challenge nuts

Specific nut Challenge	SPT positive		SPT negative	
	sIgE +ve	sIgE -ve	sIgE +ve	sIgE -ve
Almond, n=65	6		59	
	4	1	23	20
Hazelnut, n=70	4		66	
	1	1	26	21
Brazil nut, n=82	7		75	
	2	4	17	37
Cashew, n=54	6		48	
	3	1	12	21
Walnut, n=72	9		63	
	7	1	23	24
Macadamia, n=78	8		70	
	5	0	26	25

n = number of patients where nut was included in challenge biscuit. All patients had SPT prior to challenge with that nut but not all patients had sIgE measured hence the incomplete data set for sIgE results.