OPTIMISING THE DIAGNOSIS OF PEANUT AND TREE NUT ALLERGY

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ABSTRACT
Peanuts and tree nuts form an important protein source in Africa, particularly during vulnerable growth periods such as weaning and early childhood. The peanut allergy rates in Israel and countries in Africa and Asia are low, approximately 0.5%, whereas English-speaking westernised countries have higher rates of 1.3-1.5%. It is possible that these low rates of peanut allergy may well increase as dietary and environmental changes alter to more closely reflect those of westernised countries. Nut allergy is a particularly troublesome condition as it is seldom outgrown and is associated with considerable morbidity and mortality. It is therefore important to make optimal use of the diagnostic modalities available to the clinician in order to facilitate the most accurate diagnosis, as well as to best implement prophylactic and/or treatment strategies. Diagnostic modalities available include a comprehensive clinical history, physical examination, skin-prick tests (SPTs) and specific IgE assays. Despite the optimal use of these investigations many patients still require an oral nut challenge to confidently establish a diagnosis of nut allergy or tolerance. The largest deficit in our diagnostic armamentarium remains the lack of universal access to oral food challenge tests. Only when sufficient data are available from African centres that perform oral food challenges will the performance characteristics of the SPT and specific IgE tests be open to validation for use in this setting.

BACKGROUND
The prevalence of peanut allergy (PA) in Africa is unknown but anecdotal reports suggest the prevalence to be lower than that experienced in developed countries, which report a prevalence of approximately 1.5%. Countries in Africa and Asia, as well as Israel, where the early consumption of high-dose peanut protein is routinely practised, have enjoyed a low prevalence of peanut allergy, e.g. 0.04% in Israel. There is evidence that the prevalence of peanut allergy continues to increase among high-risk atopic infants, as well as among children in the general population. The prevalence of tree nut allergy has not been independently assessed among general populations, but studies of adults and children with peanut allergy suggest a high co-prevalence. Peanuts and tree nuts, often generically referred to as ‘nuts’, combine to form an important protein source in Africa, particularly during vulnerable growth periods such as weaning and early childhood. Given the accessibility, affordability and acceptability of peanuts as a food source, they now constitute the main source of protein used in feeding schemes throughout the world. Peanuts are also consumed by certain ethnic groups in the cultural belief that the early consumption of peanuts increases virility. Given the steadily rising prevalence of allergic disease among all African populations, and with global evidence that a rise in food allergies has accompanied the overall increase in allergies, we should anticipate a rise in the prevalence of peanut and tree nut allergies in Africa. Anecdotally our observation in an inner-city London hospital is that the rates of peanut allergy have increased remarkably in ethnic populations in whom peanut allergy was not a problem 5-10 years ago.

SIGNIFICANCE OF PEANUT ALLERGY
Peanut and tree nut allergy are particularly troublesome food allergies as patients rarely outgrow them and they are associated with considerable morbidity and mortality. Nut allergies are now the most frequent cause of food-induced anaphylaxis in westernised countries. Community-based anaphylaxis admissions among the general UK population have doubled over the period 1991-1995. Children and families have to be cautious about their eating habits. The fear of a potential allergic reaction and the necessity of having to carry emergency medication at all times, as well as the stigmatisation of children with peanut allergies, have been shown to markedly reduce the quality of life of both the peanut-allergic patient and the family. The effects on an infant of eating peanut butter (generalised urticaria and angioedema) are shown in Figures 1 and 2.

MODALITIES AVAILABLE FOR MAKING A DIAGNOSIS OF NUT ALLERGY
In order to accurately identify those at risk of future reactions as well as to best implement prophylactic and/or treatment strategies, we need to most accurately identify those individuals with, or at increased risk of developing, nut allergy. The clinician has numerous modalities available for making the diagnosis of ‘nut’ allergy; these include clinical history, physical examination, skin-prick test (SPT), specific IgE assays and oral food challenge. The oral food challenge is the only diagnostic test that is not currently available to the majority of clinicians in South Africa.

Does the lack of access to oral food challenge tests limit our diagnostic ability when making the diagnosis of ‘nut’ allergy?
This question is best answered through the analyses of studies performed where the diagnosis of ‘nut’ allergy is made without an oral food challenge test. One such study was recently published by Clark and Ewan in which they present a large observational cross-sectional study of children and adults referred to a specialist allergy clinic, all having experienced an allergic reaction to at least one nut. We reviewed this article in a recent editorial and interesting aspects are again highlighted. History, SPT and nut-specific IgE (CAP) tests were performed for peanut and up to four tree nuts (Brazil nut, almond, hazelnut and walnut extracts). In the absence of an oral food challenge, the authors chose to clarify the interpretation of SPT and specific IgE tests using a clear history. The detailed clinical history was graded.
for severity, and all equivocal nut allergy cases were excluded, either on clinical grounds, or if the food was not definitely known to contain nut.

The study highlights both the advantages and limitations of the diagnostic modalities currently available to clinicians for the diagnosis of peanut and tree nut allergies. The clinical history is important for diagnosis, but the performance of this investigation when compared with oral food challenges may not be optimal. In general, studies that make use of the oral food challenge to establish a diagnosis of food allergy reveal that a comprehensive clinical history may only be validated in less than 50% of patients. This much-disputed discrepancy between a detailed history of food allergy and oral food challenge outcome is somewhat surprising. One potential explanation is that food allergy studies frequently include young children with egg and cow’s milk allergy. Unlike peanut allergy, egg and cow’s milk allergy usually resolve early in life; therefore, unless oral food challenges are performed within the first few years of life, negative results are to be expected. Other reasons for negative oral food challenges in the face of a suggestive history include: confusing histories, misidentification of food in the history and non-allergic causes of symptoms.

Physical examination

The physical examination is also an important diagnostic modality, as the ‘allergic phenotype’ of the individual influences not only the choice of allergy test, but also its interpretation. Patients with atopic eczema dermatitis syndrome (AEDS) are commonly peanut allergic and characteristically have high total IgE, both factors known to influence the predictive performance of allergy tests. In addition, extensive eczematous lesions may limit the opportunity to perform an SPT on unaffected skin. A clinical diagnosis of asthma is also an important physical finding, as most patients with fatal or near-fatal anaphylaxis have concomitant asthma.

Allergy tests

SPTs have been used as an in vivo allergy investigation for over a hundred years, but are seldom performed by non-allergists. Specific IgE tests are therefore usually performed for the diagnosis of peanut and tree nut allergy. The initial radio-allergosorbent tests (RAST) have largely been superseded by the use of enzyme-linked immunosorbent assays (ELISA). Recent predictive studies have made use of the CAP specific IgE assays (CAP System FEIA; Pharmacia-Upjohn Diagnostics), shown to be reproducible, standardised and quantifiable across a broad range of IgE values.

CLARK AND EWAN’S STUDY

While Clark and Ewan’s study does not make use of oral food challenges, the authors make the point that 10 000 oral food challenges would have been required to analyse the five-nut allergic status of 1 000 patients (n=1 000, five-nut challenge with placebo). Instead they therefore rely on a very careful history.

In their study population peanut was responsible for the majority of index reactions (58%) followed by Brazil nut (16%) and hazelnut (6%). Peanut reactions were more likely to be classified as mild (61%) and Brazil nut allergic moderate to severe (68%). An important finding is that 46% of patients who were sensitised to a non-index nut reported histories of tolerance to that nut. Up to 56% of patients allergic to one nut were able to tolerate another type of nut.

In keeping with existing peanut allergy data, Clark and Ewan’s study could establish no correlation between severity of reaction and magnitude of SPT diameter or specific IgE CAP level. Interestingly, for Brazil nut alone, there was an increase in SPT diameter if severe reactions were compared with all mild to moderate reactions (p=0.0005). Brazil nut allergic patients with the most severe reactions had larger SPT wheals. The selective relationship seen between Brazil nut clinical reactivity and the magnitude
of SPT result could in theory be explained by the characteristics of the allergens within the Brazil nut SPT solution. Brazil nut is an uncommon example of an allergen source where a single major allergen (2S albumin) is responsible for clinical reactivity.26 This is in contrast to most allergenic foods (e.g. egg, cow’s milk and peanut) where several major and minor allergens are responsible for clinical symptoms.27 Therefore, if we were to use standardised SPT solutions containing known amounts of major allergen, we might expect to see correlations emerge between severity of the allergic response and size of the test result.

Studies to date demonstrate that by careful interpretation of the magnitude of SPT and specific IgE responses, the need to perform oral food challenges can be reduced by 40% or more.28,31 These studies have mainly been performed for egg, milk and peanut. There is general consensus that negative SPTs or negative specific IgE results are consistent with clinical reactivity.28 This is in contrast to most allergenic foods (e.g. egg, milk and peanut) where several major and minor allergens are responsible for clinical symptoms.27 Therefore, if we were to use standardised SPT solutions containing known amounts of major allergen, we might expect to see correlations emerge between severity of the allergic response and size of the test result.

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Comparison with other studies

Not all studies to date agree on the cut-off SPT and specific IgE values required to achieve high positive predictive values (PPV). Sporkin et al.21 demonstrated a PPV >95% for peanut SPT wheal diameters ≥8 mm. Sampson and Ho23 set the threshold value for peanut-specific IgE concentrations at 15 kU/L for a PPV of 95%. In a subsequent prospective study Sampson25 demonstrated that the threshold value of 14 kU/L achieved a PPV ≥95%. Rance et al.26 in a larger study population, achieved a sensitivity of 44% and a specificity of 95.2% for the same threshold value of 14 kU/L. For their study population, they indicated certainty that the child was allergic to peanut only if the raw peanut SPT extract induced a wheal diameter of 16 mm or if the specific IgE was 57 kU/L (PPV 100%, sensitivity of 27.7% and a specificity of 100%). Although such high predictive values are helpful if achieved, most peanut-allergic patients present with smaller/worse test values, thereby decreasing the PPVs. Although the purpose of Clark and Ewan’s study27 was not to establish predictive values, they interestingly obtain similar specific IgE and SPT results to Sampson25 and Sporkin et al. In addition, Clark and Ewan28 establish similar predictive cut-off SPT and specific IgE values for all five nuts tested (peanut, Brazil nut, almond, hazelnut, walnut). The observations that the same allergy tests perform differently between centres may be due to many factors. Firstly, although the sensitivity, specificity and efficiency of a diagnostic test provide information about the ability of allergy tests to identify nut allergy, most clinicians prefer working with positive and negative predictive values. The calculation of predictive values is, however, influenced by the population prevalence of nut allergy, which may differ between tertiary allergy centres.29 The performance of predictive values may therefore not be applicable across all populations. For example, Rance et al.’s26 study population had a peanut allergy prevalence of 48.8%, Sampson’s29 81% and Clark and Ewan’s study population a peanut and tree nut allergy prevalence of 100%, as this was the principal reason for referral. Likelihood ratios, on the other hand, although less frequently utilised for the interpretation of allergy results, have the advantage of being independent of the population prevalence of the condition being studied.30 The population prevalence of peanut allergy is influenced by the allergic phenotype of the study population. The highest prevalence of peanut and tree nut allergy is found in children with moderate to severe AEDS30-32 whereas patients with chronic idiopathic urticaria share the same food allergy prevalence as the general population.33 The allergic phenotype varies between published predictive studies; for example, Rance et al.’s26 study was conducted among a population of children with a wide range of symptoms (AEDS, urticaria, angioedema, asthma and anaphylactic reactions) typical of those seen in patients with peanut allergy. Sampson and Ho’s34 retrospective study population of 196 children and adolescents all had AEDS and approximately 50% had asthma and allergic rhinitis. Sampson’s prospective study35 consisted of children with a mix of AEDS (61%) and asthma (50%).

Different reference standards used to make the diagnosis of peanut allergy between studies may also account for the different performance of allergy tests. Most predictive studies have made use of either an oral food challenge or DBPCFC as the reference standard. However, most allergy centres are reluctant to perform oral food challenges on patients younger than 3 years, and will, in addition, exclude individuals with a history of severe anaphylaxis, recent allergic reaction and uncontrolled asthma. Although these precautions are clinically prudent, the omission of highly allergic individuals may bias the sample, as it is unknown which patients among those excluded will pass or fail an oral food challenge. Predictive studies make use of different diagnostic modalities; for example, Sampson’s prospective study35 of 68 children made the diagnosis of peanut allergy by means of oral food challenge in only 2% of patients, on the basis of a suggestive history for 13% and on the basis of a convincing history for 85%. In contrast, Rance et al.’s study population36 of 363 children all underwent DBPCFCs. Clark and Ewan37
made use of a clear history for the diagnosis of peanut and tree nut allergy. The age of the study population may also be important when establishing predictive SPT and specific IgE values. Sporik et al.15 determined that for children aged 2 years or younger, 100% specificity was reached at a lower SPT wheal diameter of 4 mm. SPT histamine wheal diameters are also known to increase by 125% from 4 days to 2 years, and 50% from ages 2 to 18 years.38 Variations in specific IgE levels may also need to be considered when establishing predictive cut-offs, as they are characteristically low at birth (<2 kU/L) and increase until 10-15 years of age.39 Although Clark and Ewan’s15 study enrolled children and adults, 58% were less than 10 years of age and 36% were under 5 years old. In contrast, the Rance et al.,40 Sampson29 and Sporik et al.5 study populations all share a slightly younger median age of approximately 3 years. The young age of these study populations reflects the usual age of onset of peanut allergy at around 14 months, and tree nut allergy at around 36 months of age.42

The different performance of SPTs between studies may also be due to the unique characteristics of the SPT extracts used. That Rance et al.29 obtained larger peanut SPT wheal diameters when using raw extracts (median 6 mm, range 0-25 mm) compared with commercial extracts (median 3 mm, range 0-16 mm) is interesting, as most commercial extract manufacturers make use of raw peanut proteins (personal communication: Pharmacia UK, SJ Maleki). The performance characteristics of the two extracts also differ when compared with DBPCFC-proven peanut allergy; commercial SPT extracts were falsely negative in 18% of 32 subjects (sensitivity 82%) whereas raw SPT extracts were always positive (sensitivity 100%). Variability in SPT extracts is not unique to smaller research laboratories, as commercial peanut SPT solutions may vary by as much as 2 logs.41 Given that nut extracts are a complex mixture of proteins, lipids, carbohydrates and pigments with varying allergen concentrations, purity and degree of contamination, it is not surprising that variability occurs. Even the choice of peanut plant species may influence the quality and quantity of extract allergens.42 The process of roasting or frying has been shown to significantly alter the allergenic properties of peanut.43 Maleki et al.17 demonstrated that roasted peanut samples are less soluble, more resistant to digestion, and bind significantly higher levels of serum IgE from peanut allergic individuals. In addition, roasted peanut SPT extracts result in larger wheal diameters than raw peanut extracts. Many of these novel characteristics are attributable to the Maillard reaction, a heat-induced, non-enzymatic biochemical reaction between reducing sugars and amino acids.44 Therefore, given that humans generally consume peanuts after boiling, frying or roasting, it may be clinically more relevant to make use of roasted peanut extracts for SPT and specific IgE testing. This may however not be true for patients with oral allergy syndrome (OAS), a condition characterised by oro-pharyngeal symptoms secondary to cross-reactivity between ingestable allergens and aeroallergens.45 For example, patients allergic to birch pollen may show symptoms after the ingestion of raw vegetables and fruits such as potatoes, carrots, celery, apples, pears and kiwi.46 Of note is that tree nuts such as hazel,47 almond47 and walnut48 have been incriminated as cross-reactive OAS allergens. For these patients, SPT reactivity may only be demonstrated if use is made of fresh SPT extracts or by performing the SPT in a prick plus prick method.49

Specific IgE assays are also subject to variability with the result that many of the commercial assays available are not always interchangeable or equivalent. Even the CAP system, which achieves greater quantification and better inter-assay agreement through standardised calibration schemes, remains subject to a degree of variability.50,51 Given all these variables, it may be necessary to standardise SPT extracts and reagents used in specific IgE assays not only in respect of major allergen content but also the processed form of the protein. The use of recombinant allergens for allergy testing certainly offers benefits with regard to the standardisation of major allergens. However, as these proteins lack natural post-translational modification such as glycosylation, they may respond differently to heat processing when compared to native allergens, rendering them less biologically relevant.

**RECOMMENDATIONS**

We therefore need to continue in our efforts to optimise the clinical and laboratory diagnosis of nut allergy. Currently the largest deficit in our diagnostic armamentarium in South Africa remains the lack of access to oral food challenge tests. This limits patient management for the many individuals with an equivocal history of having had a nut-induced reaction who have poorly predictive allergy test results. To remedy this deficit, the broader medical community needs to support ALLSA in their longstanding effort to develop and expand the discipline of allergy in Southern Africa. Academic centres should ensure that appropriate facilities exist in which to perform oral food challenges, which are safe when performed in experienced hands and in a controlled environment. In addition, private health care funders need to recognise that despite the labour-intensive nature of oral food challenges they remain a cost-effective investigation designed to optimise patient care and safety. Only when sufficient data are available from African centres that perform oral food challenges will the performance characteristics of our existing allergy tests be open to validation for use in this setting. This is especially necessary for African populations, who are often destined to experience a low prevalence of nut allergy but who are at risk of following the increasing trends experienced in westernised countries.

Informed consent was obtained for use of patient photographs.

**REFERENCES**

ERRATA

Computer-generated printer's gremlins seem to be as prevalent as the old-fashioned kind. In the March issue two unfortunate errors occurred. On the contents page, p.1, the authors of the article 'Accurate diagnosis of latex allergy in hospital employees is cost-effective' were incorrectly given as the same as the authors of the first article. The correct authors are C de Beer and J Cilliers. We apologise to all concerned.