

The concordance between component tests and clinical history in British adults with suspected pollen-food syndrome to peanut and hazelnut

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ABSTRACT

Background Mild oropharyngeal symptoms to peanut/hazelnut occur in ~30% of patients with pollen-food syndrome (PFS). Component tests are considered a useful adjunct to the diagnosis and may help differentiate PFS from those at a risk of anaphylaxis due to storage protein/lipid transfer protein (LTP) sensitisation.

Aims To assess concordance between component tests and clinical history in suspected PFS to peanut/hazelnut in a specialist clinic.

Methods Adult patients were classified into PFS (group 1, n=69) and PFS with mild systemic symptoms (group 2, n=45) based on clinical history. Specific IgE (sIgE) of ≥ 0.35 kUA/L was considered positive as per manufacturers' recommendation. Kappa (κ) inter-rater agreement was calculated for concordance between clinical classification and test profiles.

Results Group 1 hazelnut: 85% monosensitised to Cor a1, 12% to storage protein/s or LTP and 3% negative to all components. Group 1 peanut: 41% monosensitised to Ara h8, 44% to storage protein/s or LTP and 15% negative to all components. Group 2 hazelnut: 67% monosensitised to Cor a1, 16% sensitised to storage protein/s and 17% negative to all components. Group 2 peanut: 19% monosensitised to Ara h8, 62% sensitised to storage protein/s and/or LTP and 19% negative to all components. sIgE to Ara h8 and Cor a1 were greater in group 1 versus group 2: (median (IQR) kUA/L; hazelnut: 12.1 (7.8-25.2) vs 2.4 (0.36-6.3), $p<0.001$; peanut: 2.4 (0.10-21.1) vs 0.3 (0-3), $p<0.01$).

Conclusion Concordance between component tests and clinical history for adults with PFS was good for hazelnut ($\kappa=0.63$) but poor for peanut ($\kappa=0.12$). Food challenges are warranted in discordant cases for an accurate diagnosis.

INTRODUCTION

It is estimated that 50%–90% of patients in Europe with birch pollen allergy suffer from pollen-food syndrome (PFS).^{1,2} It has been reported to affect 66% of British patients with birch pollen allergy with an estimated UK general population prevalence of 4.3%.^{3–5} PFS is a consequence of the cross-reactivity of specific IgE (sIgE) between birch pollen antigens and heat labile proteins (PR-10, profilins) present in plant foods (eg, fruits, vegetables, peanuts, hazelnuts and almonds). The disorder is characterised by relatively mild oropharyngeal allergic reactions with patients typically tolerating the cooked versions of the implicated fruits

and vegetables.^{3,4} Clinical assessment of the vast majority of patients with allergic reactions to fruits and vegetables is relatively straightforward but may be more complex in those reacting to peanut and/or hazelnut.

'Primary' peanut and hazelnut allergy is linked to sensitisation to storage protein/s.^{6–8} This is more common in children and occurs less frequently in adults. The 'secondary' form or PFS phenotype is a cross-reactive allergy between Bet v1/Bet v2 and PR-10 homologue/profilins, respectively, and is usually associated with birch pollen allergy.⁹ Less commonly, clinical reactivity may be a consequence of sensitisation to non-specific lipid transfer protein (nsLTP) in peanut and hazelnut, and these may cause systemic reactions/anaphylaxis.¹⁰

The advent of sIgE tests to recombinant allergen components has created an opportunity to delineate the sensitisation profiles to storage proteins, nsLTP and PR-10 and, thus, may aid in the process of risk stratification. Although sensitisation to storage protein/s and/or nsLTP is linked to systemic reactions/anaphylaxis, monosensitisation to PR-10 proteins is associated with PFS.² Component sIgE tests are not routinely required in patients with a clear history of anaphylaxis or systemic reaction with demonstrable sensitisation by skin prick test (SPT) or serum sIgE to the whole allergen. However, they may serve as a useful adjunct test to assist clinical management in those that present with suspected PFS or in patients with an indeterminate clinical history in order to exclude sensitisation to storage protein/s and/or nsLTP.

Studies have shown that sIgE assay to Ara h2 (conglutin, a major peanut antigen) is currently the most reliable diagnostic test for peanut allergy.¹¹ It carries high sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV).¹¹ Furthermore, there is also some evidence that a higher sIgE concentration to Ara h2 correlates with a greater risk of severe systemic reactions/anaphylaxis.^{11,12} In contrast, sensitisation to Ara h8 (PR-10, Bet v1 homologue) without a positive sIgE to Ara h2 makes PFS or a milder clinical phenotype more likely.¹² Similarly, the presence of sensitisation to Cor a9 or Cor a14 (storage protein antigens in hazelnut) is linked to more severe hazelnut reactors and monosensitisation to Cor a1 (PR-10 in hazelnut) with PFS.^{7,13}

The performance of these tests is influenced by a number factors, in particular, age, patient selection,



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geographical region and pollen sensitisation.¹¹ Most evidence comes from studies in children with a 'primary' form of allergy, which were conducted in Northwestern Europe, Mediterranean countries and North America.¹¹ Currently, there is paucity of published literature on the performance of component tests in adults with 'secondary' form (PFS) of peanut allergy and hazelnut allergy.

Double-blind placebo-controlled food challenge (DBPCFC) or oral food challenge (OFC) remains the gold standard test for an accurate diagnosis and categorisation of patients into PFS or systemic phenotypes. This procedure is, however, resource dependent and time consuming, and it carries a risk of provoking anaphylaxis. Although DBPCFC is an essential research tool, it is performed less often in a routine clinical service setting and is subject to staffing and financial constraints.¹⁴ This is particularly relevant to the UK National Health Service (NHS) where there is currently an unmet need for specialist allergy services.^{5 15} Hence, our current practice involves obtaining an accurate clinical history followed by determination of sensitisation to whole peanut and hazelnut extracts. Component tests are only requested for patients with suspected PFS or when historical information is inadequate or indeterminate. A 'cut-off' of ≥ 0.35 kUA/L is used for sIgE, and patients are stratified as 'high risk' if there is demonstrable sensitisation to storage protein/s and/or nsLTP

and 'low risk' if there is monosensitisation to PR-10 proteins (ie, negative sIgE to storage protein/s and nsLTP) in conjunction with a history of PFS.

The main aim of this study was to assess the degree of concordance between component tests and clinical presentation in adults presenting with suspected PFS to peanut and/or hazelnut in a routine clinical setting of a specialist allergy clinic.

METHODS

This study was conducted in Heart of England NHS Foundation Trust (HEFT). An electronic search on laboratory database (Telepath, ISOFT) was conducted for the period 1 January 2013 to 31 May 2016 to identify patients (≥ 17 years) who were investigated with sIgE component tests for peanut and hazelnut allergy *via* the adult specialist allergy service.

Data on patient demographics, characterisation of the allergic reaction and component test results were extracted from electronic patient records by the same operator (SCB) in a standardised format and transcribed electronically on to MS Excel spreadsheet. Patients were categorised into two groups (figure 1) based on the pattern of clinical reactivity: group 1 reported mild oropharyngeal symptoms only to peanut or hazelnut and met the criteria for PFS (adapted from a recent British study by

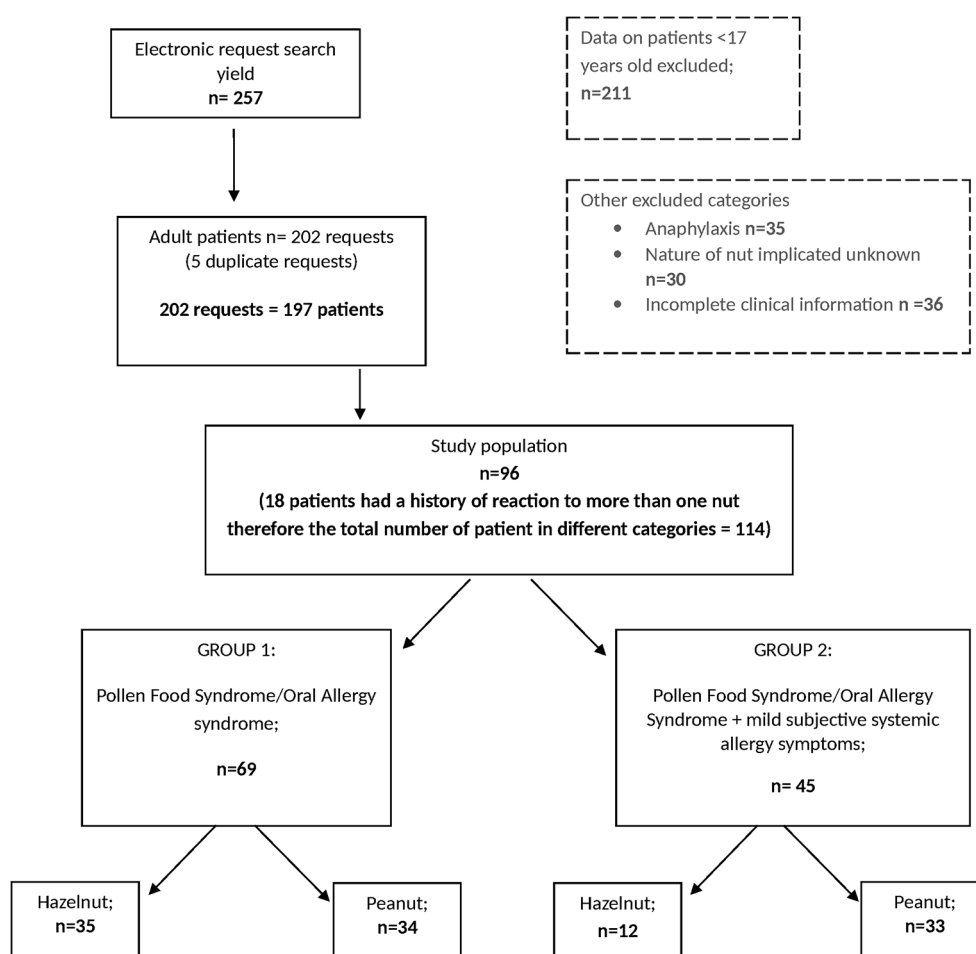


Figure 1 Study flow diagram; clinical categories 1 and 2 adapted from Skypala *et al.*⁴ Group 1: localised oropharyngeal only: (tingling/numbness of lips/mouth or a strange sensation, itching of the lips, mouth, palate or ears, scratchy/sore throat, swelling of lips, tongue, mouth or throat). Group 2: localised as in group 1 and mild systemic reaction (nasal congestion, sneezing, itchy nose, nasal blockage, itchy/watery eyes, red eyes, chest tightness, mild wheeze—no treatment, localised rash, heart burn, abdominal discomfort, diarrhoea, nausea and vomiting). CRD, component resolved diagnostics.

Table 1 Components tested for hazelnut and peanut

Hazelnut components	Allergen type	Heat stability	Peanut components	Allergen type	Heat stability
Cor a1	PR-10	No	Ara h1	Storage protein	Yes
Cor a8	Non-specific lipid transfer protein	Yes	Ara h2	Storage protein	Yes
Cor a9	Storage protein	Yes	Ara h3	Storage protein	Yes
Cor a14	Storage protein	Yes	Ara h8	PR-10	No
			Ara h9	Non-specific lipid transfer protein	Yes

Skypala *et al*)—patients reported mild symptoms limited only to the oropharynx or ears.⁴ Group 2 described symptoms of PFS and mild (mostly subjective) symptoms suggestive of a possible systemic involvement but did not meet the criteria for anaphylaxis as per World Allergy Organisation (WAO) diagnostic criteria.¹⁶ Mild systemic symptoms included nasal congestion, sneezing, itchy nose, itchy/watery/red eyes, chest tightness/wheeze not requiring treatment, localised rash and abdominal symptoms, including pain, diarrhoea, nausea and vomiting. Details of clinical categorisation of groups 1 and 2 are summarised in [figure 1](#).

Patients with anaphylaxis (as per WAO clinical criteria for anaphylaxis)¹⁶ were excluded from the analysis to avoid selection bias because our clinical service does not routinely request component tests in this group. These patients may have had these tests on an exceptional basis or due to patient-specific factors, and hence, would not constitute a true representative sample. Patients with incomplete clinical information regarding severity of the index reaction and/or nature of nut implicated were also excluded from the analysis. Categorisation of clinical groups was validated by selecting 20 random patients from the cohort and demonstrating 100% concordance between the lead investigator (SCB) and a second operator (MTK).

Analysis of serum total IgE and peanut and hazelnut components ([table 1](#)) was performed on ImmunoCAP 250 (Thermo Fisher Scientific, Waltham, Massachusetts, USA). sIgE values ≥ 0.35 kUA/L were considered positive as per manufacturers' recommendation.

All patients underwent tests to a full panel of peanut components. However, not all underwent testing to the complete panel of hazelnut components because the storage protein immunoCAPs (Cor a9 and Cor a14) only became available in the UK NHS laboratories from 2014. Of 35 patients, 32 (91%) from group 1 were tested to a full panel of hazelnut components (Cor a1, a8, a9 and a14). All patients were tested for Cor a1 and Cor a8.

Statistical analysis

Statistical analysis was performed using MedCalc (version 17.0.4; MedCalc software bvba, Ostend, Belgium).

The D'Agostino-Pearson test for normal distribution was performed for Ara h8 and Cor a1 sIgE concentrations. As normality was rejected, the Mann-Whitney U test was used to compare concentrations between groups 1 and 2.

The kappa inter-rater agreement was calculated for concordance between the clinical classification groups and the component test profiles for hazelnut and peanut. The following rules were used: component test profile was consistent with group 1 if there was monosensitisation to Ara h8 (with negative sIgE to Ara h1, Ara h2, Ara h3 and Ara h9) or Cor a1 (with negative sIgE to Cor a8, Cor a9 and Cor a14) for peanut and hazelnut, respectively. For group 2, a consistent profile was dependent on sensitisation to a storage protein/s (Ara h1, Ara h2 or Ara h3 for peanut and Cor a9 or Cor a14 for hazelnut) or nsLTP (Ara h9

for peanut and Cor a8 for hazelnut) regardless of Ara h8 and Cor a1 sensitisation. The κ value ranges from -1.0 to $+1.0$; the higher the value, the stronger the agreement; low negative values (0 to -0.1) represent no agreement, and large negative values (<-0.1) represent great disagreement.

The study proposal was submitted to the research and development department in HEFT, who confirmed that formal ethics approval was not needed, and the project was registered with the clinical governance unit in HEFT.

RESULTS

The consort diagram is shown in [figure 1](#), and patient demographics are summarised in [table 2](#).

Hazelnut group 1

The overall sensitivity for Cor a1 for hazelnut-related PFS was 97%. This is higher than whole hazelnut sIgE, which was positive in 87%.

[Figure 2](#) summarises the sensitisation profile of patients in group 1. The one patient who was negative for all hazelnut components had a negative skin prick test to whole hazelnut extract; however, the sIgE to whole hazelnut was only weakly positive at 0.42 kUA/L.

None of the patients sensitised to nsLTP or storage proteins in this group described clinical symptoms of a systemic nature.

Hazelnut group 2

The sensitisation profile for this group is summarised in [figure 2](#). A lesser proportion (67%) of patients were monosensitised to Cor a1 with 16% sensitised to storage protein/s and 17% negative to all components tested. The latter were also negative to SPT and sIgE to the whole hazelnut extract.

Peanut group 1

The sensitisation profile is summarised in [figure 3](#).

While 14/34 (41%) were monosensitised to Ara h8, 8/34 (23%) were also sensitised to a storage protein.

Of the five patients who were negative to all components, three had a positive SPT to whole peanut extract. Two of the five had a positive sIgE to whole peanut; however, it is notable that the remaining three had an sIgE concentration between 0.20 and 0.35 kUA/L.

The sensitivity of Ara h8 in group 1 was low (65%). This was lower than the sensitivity to whole peanut (82%)

Peanut group 2

There were 32 patients in group 2 and the data are summarised in [figure 3](#). Six patients (19%) showed no sensitisation to any of the peanut components. Two of these patients had a positive SPT (>4 mm) to whole peanut extract, two were negative and two were not tested. As regards serum sIgE to whole peanut allergen,

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Table 2 Patient demographics

	No of patients	M:F	Age, mean (SD), years	Total IgE concentration, median (IQR)	Percentage of group with positive sIgE to whole nut*	Percentage of group with hay fever†
Total, group 1	69	22:47	34.5 (12.8)	203 (99–519)	85	
Group 1 hazelnut	35 (12 patients had an additional category)	9:26	35.9 (12.8)	204 (84–437)	87	95
Group 1 peanut	34 (9 patients had an additional category)	13:21	32.7 (12.7)	204 (117–836)	82	75
Total, group 2	45	18:27	30.50 (13.1)	264 (128–412)	77	
Group 2 hazelnut	12 (4 patients had an additional category)	3:9	38.2 (15.4)	133 (82–314)	75	86
Group 2 peanut	33 (5 patients had an additional category)	15:18	25.7 (9.2)	295 (164–412)	78	63

*Positivity based on specific IgE to whole hazelnut or peanut of ≥ 0.35 kUA/L, 109/114 patients tested.

†A complete data set regarding hay fever was not available from clinical records of all patients in the cohort; total number of patients in each group: group 1 hazelnut n=22; group 1 peanut n=26; group 2 hazelnut n=8 and group 2 peanut n=27.

sIgE, specific IgE.

2/6 patients were positive (both were SPT negative) and 4/6 were negative.

Cor a1 and Ara h8 concentrations

The concentration of Cor a1 and Ara h8 was compared between groups 1 and 2 (figure 4). They were significantly higher in group 1 ($p<0.001$ for hazelnut and $p<0.01$ for peanut).

Kappa statistics of concordance

Concordance between the component profile and the clinical presentation for hazelnut was good with $\kappa=0.63$ but poor for peanut $\kappa=-0.12$.

DISCUSSION

This is the first study investigating the clinical utility of component tests in a 'real-world' clinical setting in adults presenting with suspected peanut-related or hazelnut-related PFS. The two clinical groups chosen in this study represent the diagnostic conundrum faced by an allergy specialist in routine clinical practice. The data set shows that the concordance between component test sensitisation profiles and clinical history was good for hazelnut but poor for peanut.

The data showed that 85% of patients who described mild oropharyngeal symptoms to hazelnut were monosensitised to Cor a1. However, 12% (n=4) were also sensitised to a storage protein or Cor a8 (LTP), which is not consistent with an expected pattern of hazelnut-related PFS. Two out of four patients were dually sensitised to Cor a9 and Cor a14 with sIgE levels of 0.66 and 57.8, and 1.29 and 34.2 kUA/L, respectively. The clinical significance of these data can only be confirmed with an OFC. It is plausible that these patients are at a risk of anaphylaxis to a hazelnut challenge. It is also possible that these patients are at no increased risk and the tests were false positive.

The data set for patients in groups 1 and 2 of peanut showed an interesting pattern of sensitisation. Only 41% of patients in group 1 were monosensitised to Ara h8. This is a relatively low proportion because peanut-related PFS is a consequence of cross-reactions between birch pollen sIgE and Ara h8. Importantly, 44% of patients in group 1 showed sensitisation to peanut storage protein/s or Ara h9 (nsLTP), increasing the odds of anaphylaxis to a peanut challenge. It is, however, also plausible

that these patients are at no increased risk and the tests were false positive. A peanut OFC is required for an accurate risk stratification.

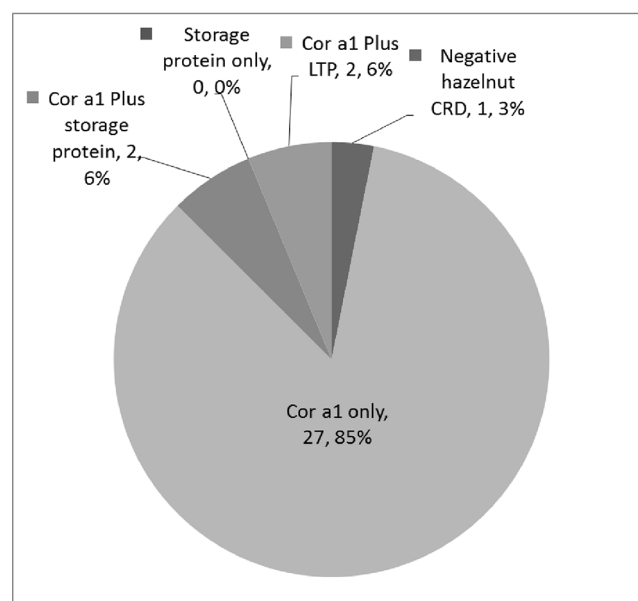
A significant proportion (62%) of patients in group 2 were sensitised to a storage protein/s or Ara h9 (nsLTP) raising the probability of anaphylaxis to peanut. Furthermore, our data also showed that 15% (n=5) of patients in group 1 and 19% (n=6) in group 2 were negative to all peanut components tested, despite reporting significant symptoms on peanut exposure.

In patients sensitised to peanut storage proteins regardless of clinical presentation, Ara h2 (n=42; 93%) was the most frequent antigen as reported previously.¹¹ In other words, only 7% (3/42) were positive to Ara h1 or Ara h3 and negative to Ara h2 (figure 5).

Another interesting observation in this study is that the sIgE concentration of Ara h8 and Cor a1 was significantly greater in group 1 compared with group 2 for peanut and hazelnut, respectively. This is in keeping with previous studies which have shown that sensitisation to Ara h8 correlates with relatively mild allergic reactions (PFS phenotype) or indicates clinical tolerance in birch pollen endemic areas and in Asian countries, respectively.^{11 12 17}

This study has limitations. First, it was retrospective involving extraction of data from clinical records generated by multiple clinicians. However, it involved the same clinical service with a standardised approach in place with respect to history taking, documentation and allergy investigation protocol. The data collection was undertaken by a single operator and validated with a second experienced observer by demonstrating 100% concordance on a randomly selected cohort of 20 patients with respect to categorisation into respective clinical groups. Second, it is limited by a relatively small sample size. Third, peanut and hazelnut challenges were not conducted because of service constraints, and reliance was placed on the patient's recall of the index episode. This study however highlights the important management dilemma faced by an allergy specialist in the interpretation of component allergy tests, particularly when there is discordance with the clinical presentation. At the present time, component tests to various allergens including peanut and hazelnut have been launched in the UK without appropriate clinical validation of the 'cut-off' value of ≥ 0.35 kUA/L. An ideal approach would be to determine the discriminatory decision

A: Group 1



B: Group 2

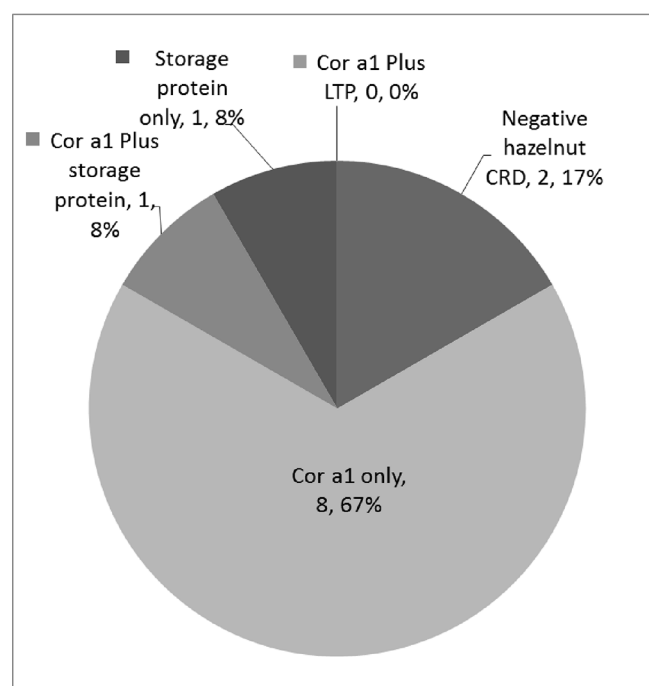
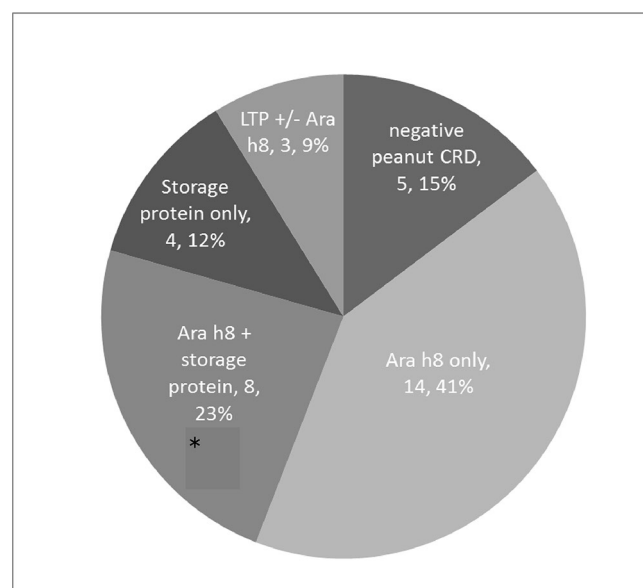


Figure 2 Pie charts showing the sensitisation profiles (number and percentage) to components in hazelnut group 1 patients (A) and group 2 patients (B). Components are divided into Cor a1, Cor a1 plus a storage protein (Cor a9 and/or Cor a14), storage protein only, Cor a1 and Cor a8 and negative to all components. Group 1, n=32 as three patients from the total of group 1 did not have hazelnut components tested. CRD, component resolved diagnostics; LTP, lipid transfer protein.

points for 100% NPV in a local population in those who are clinically tolerant or have PFS and 100% PPV and specificity for those with a 'primary allergy'. Those falling in the intermediate zone may undergo OFC or DBPCFC for risk stratification. This approach, however, would not be feasible in most UK NHS

A: Group 1



B: Group 2

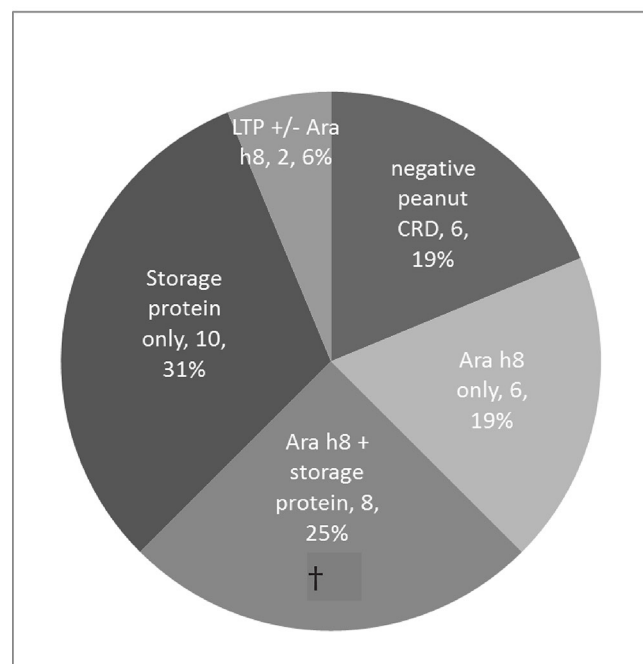


Figure 3 Pie charts showing the sensitisation profiles (number and percentage) to components in peanut group 1 (A) and group 2 (B). Components are divided into Ara h8, Ara h8 plus a storage protein (Ara h1, Ara h2 and/or Ara h3), storage protein only, LTP (Ara h9) and negative to all CRD. CRD, component resolved diagnostics; LTP, lipid transfer protein. * 3/8 co-sensitised to LTP. † 1/8 co-sensitised to LTP.

allergy clinics given the high prevalence of PFS (it is estimated that birch pollen allergy affects 5%–7% of UK subjects with PFS affecting 2%–3% of UK adult population)³ and the unmet need for allergy services. To put this into perspective further, a recent study by Skypala *et al* reported that 27% and 12% of British patients with PFS reported allergic reactions to hazelnuts and peanuts, respectively.³ With appropriate risk stratification, a process of home challenge may be possible with patients following a defined protocol for self-administration of nuts,

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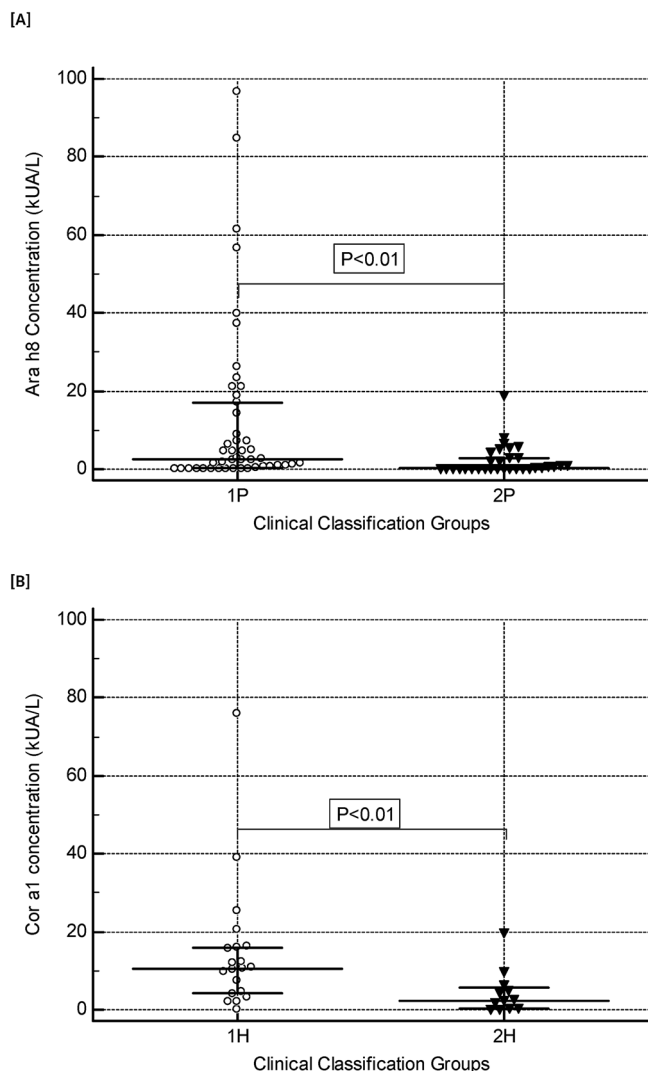


Figure 4 Dot plot showing spread of component sIgE concentrations in patients categorised as groups 1 and 2. (A) 1P = group 1 (peanut); 2P = group 2 (peanut) versus Ara h8 concentration. Median (IQR): group 1, 2.415 kU/L (0.13–21.1); group 2, 0.300 kU/L (0.00–2.95). (B) 1H = group 1 (hazelnut); 2H = group 2 (hazelnut) versus Cor a1 concentration. Median (IQR): group 1, 12.10 kU/L (7.84–25.20); group 2, 22.41 kU/L (0.36–6.33).

documentation of any reactions and communication with allergy specialists.

Previous studies involving component tests to peanut and hazelnut were limited by their heterogeneity in patient selection, selection bias, variations in protocols used for OFCs and their interpretation as well as geographical variations that impact on pollen sensitisation.¹¹ A prospective multicentre study with a larger sample size including healthy controls and DBPCFC is needed to establish performance of component tests in the diagnosis of peanut and hazelnut-related PFS. Until further data are available, OFCs should be conducted in selected patients for accurate risk stratification or alternatively, a cautious and pragmatic approach adopted in the clinical management.

Broader testing for sensitisation to a wide repertoire of whole allergens and components can be achieved by multiplex technologies such as Immuno Solid-phase Allergy Chip (ISAC,

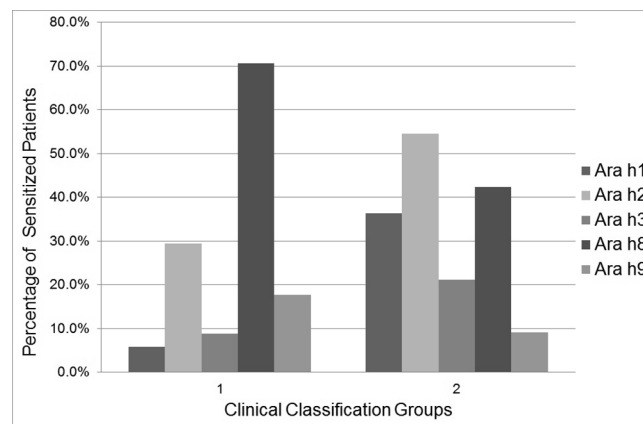


Figure 5 Frequency distribution chart showing the percentage of patients who were sensitised to peanut components. Group 1—Ara h2 positive in 10/12 (83%) of patients sensitised to storage proteins. Group 2—Ara h2 positive in 100% patients sensitised to storage proteins.

Thermo Fisher Scientific). Such tests may be useful in identifying cross-sensitisation profiles in a single analysis. This could further aid the identification of patients at risk of more severe reactions.

In conclusion, this study suggests that there was good concordance between component tests and clinical history for British adults presenting with a history of hazelnut-related PFS. The concordance was poor for those presenting with a history of peanut-related PFS. In cases with discordant results, an OFC is needed for an accurate risk stratification, but this would present significant resource implications for the clinical services.

Take home messages

- ▶ The concordance of sensitisation profiles to allergen components with clinical presentation of pollen-food syndrome was good for hazelnut but poor for peanut.
- ▶ Positive cut-off values for serum specific IgE (sIgE) to allergen components require validation by individual laboratories.
- ▶ Results of sIgE to peanut and hazelnut component tests must be carefully interpreted alongside clinical presentation, sIgE to whole allergen and skin prick tests.
- ▶ Oral food challenge remains the gold standard to stratify risk in cases where CRD results are discordant with clinical history or presentation.

Handling editor Stephen RA Jolles.

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