

Component Ana o 3 versus extract for cashew nut allergy: A diagnostic test accuracy study in adults

To the Editor,

Cashew nut allergy is a common tree nut allergy.^{1,2} In children, previous studies showed that IgE against the cashew nut component Ana o 3 has a better diagnostic value for cashew nut allergy than IgE against cashew nut extract.³⁻⁷ In adults, studies are lacking. Therefore, the aim of this study was to determine the diagnostic value of IgE against cashew nut extract and Ana o 3 in adults suspected of cashew nut allergy. In addition, the association between severity and IgE levels against cashew nut extract and Ana o 3 was assessed.

Adult patients (≥ 18 years) who visited the Department of Dermatology and Allergology of the University Medical Center Utrecht (UMCU), the Netherlands, with a clear history of anaphylaxis to cashew nut and patients with a suspected cashew nut allergy who underwent an open food challenge (OFC) were included. The reasons for a suspected cashew nut allergy were for example a past history of symptoms to cashew nut, positive provocation at earlier age or symptoms to a meal containing cashew nut. Patients were excluded from analyses if the time between IgE measurement and OFC was more than 2 years and/or if they had missing data on sIgE and insufficient serum available to determine sIgE results. This study was approved by the local ethical committee (protocol number 13-272). All patients provided informed consent.

Data on patient demographics (age, sex), allergic comorbidities (allergic rhinitis, asthma, atopic dermatitis), OFC results and serum IgE levels against cashew nut extract and Ana o 3 were retrospectively collected from patients' medical files. Anaphylaxis was diagnosed according to the Anaphylaxis guideline of the EAACI.⁸ IgE levels against cashew nut extract and Ana o 3 were determined using the ImmunoCAP platform (ThermoFisher Scientific). In patients without historic sIgE results, sIgE levels were obtained using leftover serum stored in our biobank. If possible, serum from the same timepoint was used to measure both IgE levels. Otherwise, available serum closest to the first measurement was used with a maximum of 2 years between measurements. Sensitization was defined as positive when sIgE levels were ≥ 0.35 kU/L. Typically, IgE measurements were performed prior to OFC and doctors and patients were aware of the results.

Analyses were performed using IBM SPSS Statistics (version 26.0.0.1) and RStudio (version 1.3.1093). The characteristics

between patients with cashew nut allergy and those without cashew nut allergy were described and compared statistically. *P* values $\leq .05$ were considered statistically significant. The correlation among IgE levels against cashew nut extract and Ana o 3 was calculated using Spearman's rho coefficients. The diagnostic value of IgE levels against cashew nut extract and Ana o 3 was assessed by the area under the curve (AUC) of the receiver operating characteristic (ROC) analysis. DeLong's test was used to statistically compare the AUCs.⁹ Sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) were calculated for the clinically used cutoff point and the calculated optimal cutoff point. Cutoff points above which the PPV was 100% and below which the NPV was 100% were determined in our sample. If the cutoff point for the 100% NPV was below 0.10 kU/L (the detection limit for accurately measuring IgE levels) the NPV corresponding to 0.10 kU/L was used.

The severity of cashew nut allergy was dichotomized into mild to moderate cashew nut allergy (i.e. oFASS-3 grade 1 and 2) versus severe cashew nut allergy (i.e. oFASS-3 grade 3). Differences in IgE levels between tolerant patients, patients with mild/moderate and severe symptoms were tested using Kruskal-Wallis tests. AUC was used to further explore differences in IgE levels against cashew nut extract and Ana o 3 between patients with mild/moderate versus severe symptoms.

A total of 52 patients underwent an OFC for suspected cashew nut allergy after which nine patients were excluded from analyses due to insufficient serum volume availability and two due to exceeding the maximum amount of time between IgE measurement and OFC. Two patients were included based on a clear history of anaphylaxis to cashew nut. There was no significant difference in age, sex, atopic background and severity of allergic reaction during OFC between included and excluded patients. In total, 43 patients were included in this study. Of the 43 included patients, 18 (42%) were allergic to cashew nut. Of the 18 allergic patients, 16 underwent an OFC and 2 had an anaphylactic history to cashew nut. Of all allergic patients, 16 (89%) experienced objective symptoms and 2 (11%) only subjective symptoms. When classifying the allergic patients according to the oFASS-3 classification, none of the patients experienced a mild reaction, 12 (67%) had a moderate reaction and 6 (33%) a severe reaction.

IgE levels against cashew nut extract and Ana o 3 were significantly higher in the allergic group (sIgE against cashew nut extract

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2.57 kUa/L and Ana o 3 2.65 kUa/L) than in the tolerant group (IgE against cashew nut extract 0.05 kUa/L and Ana o 3 0.01 kUa/L; both $p < .001$). The correlation between IgE against cashew nut extract and Ana o 3 was strong (Spearman's rho: 0.92).

IgE against Ana o 3 was slightly better at distinguishing between cashew nut allergic and tolerant patients (AUC of 0.95 [95% CI: 0.90–1.00]) than IgE against cashew nut extract (AUC of 0.90 [95% CI: 0.80–0.99]); p -value for comparison AUC–ROC = .05 (Figure 1). The lowest cutoff value above which PPV was 100% was 1.27 kUa/L for IgE against Ana o 3. Twenty-six percent (11/43) of the patients had an IgE level against Ana o 3 above this cutoff value. A value of < 0.10 kUa/L for IgE against Ana o 3 resulted in a NPV of 91%, and identified 47% (20/43) of patients correctly as tolerant. When these values were combined, 72% of the patients could be diagnosed as cashew nut allergic or tolerant. When we combined the 100% PPV (cutoff value IgE > 5.82) and 94% NPV (cutoff value IgE < 0.10) values for IgE against cashew nut extract, 49% (21/43) of the patients

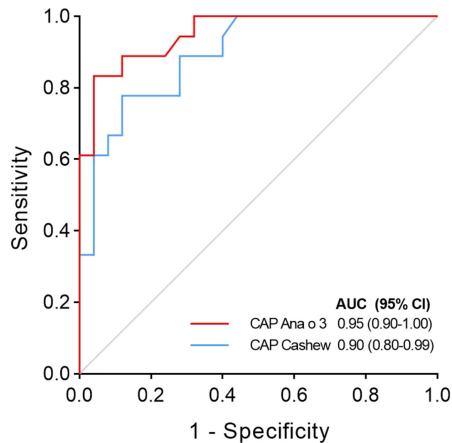


FIGURE 1 ROC-curves of IgE against cashew nut extract and Ana o 3 to predict cashew nut allergy. Abbreviations: AUC, area under the curve; CI, confidence interval; ROC, receiver operating characteristics.

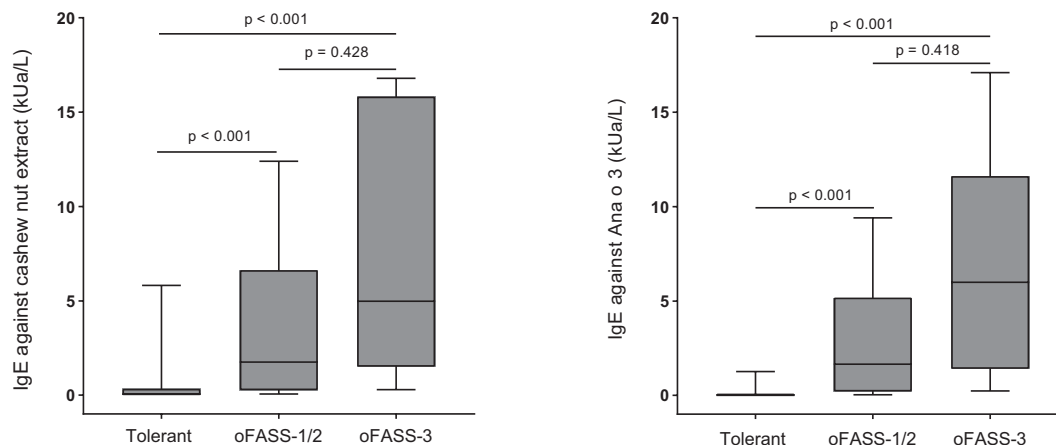


FIGURE 2 Level of IgE against cashew nut extract and Ana o 3 in tolerant patients, patients with mild to moderate symptoms (oFASS-1/2) and those with severe symptoms (oFASS-3). Abbreviations: kUa/L=kilo units of antibody per litre.

Key messages

- We undertook a diagnostic test accuracy study in 43 adults with a suspected cashew nut allergy.
- We found that specific IgE to Ana o 3 had a slightly better diagnostic performance than cashew nut extract.
- Both specific IgE to Ana o 3 and cashew nut extract did not reliably predict reaction severity.

could be diagnosed as cashew nut tolerant or allergic. Measuring IgE against cashew nut extract had no added value when Ana o 3 had already been measured.

The median IgE levels of cashew nut extract and Ana o 3 were significantly higher in the mild/moderate and severe allergic patients compared to the tolerant patients (all p -values $< .001$). Patients with a severe cashew nut allergy tended to have higher median IgE levels against both cashew nut extract and Ana o 3 than patients with mild to moderate cashew nut allergy, but this was not statistically significant ($p = .43$ vs. $p = .42$, respectively; Figure 2). The AUCs of IgE levels against Ana o 3 and cashew nut extract in predicting severity were 0.69 [95% CI: 0.43–0.96] and 0.68 [95% CI: 0.41–0.94], respectively.

This is the first study that investigated the diagnostic value of Ana o 3 versus cashew nut extract in adults. IgE against Ana o 3 was found to be superior to IgE against cashew nut extract in the prediction of cashew nut allergy which is in line with previous studies in children (AUCs IgE against Ana o 3: 0.90–0.99; IgE against cashew nut extract: 0.78–0.89).^{3–7} When combining the cutoff value for 100% PPV (1.27 kUa/L) and 91% NPV (< 0.10 kUa/L) for IgE against Ana o 3, a total of 72% of patients were diagnosed as either cashew nut allergic or tolerant. Only for patients with an IgE level against Ana o 3 between 0.10 and 1.27 kUa/L (28%) an OFC be needed. As PPV and NPV of diagnostic tools are dependent on the prevalence of cashew nut allergy in the population examined and our patient

sample was relatively small, generalizability of these cutoff values to other populations is unclear, stressing the importance of validation in other datasets.

In relation to severity of cashew nut allergy, the median IgE values against cashew nut extract and Ana o 3 were significantly higher in the allergic patients with mild/moderate and severe symptoms compared to the cashew nut tolerant patients. Although levels of IgE against cashew nut extract and against Ana o 3 tended to be higher in patients with severe reactions compared to patients with mild to moderate reactions, this was not statistically significant. This might be due to the small number of cashew nut allergic patients (12 patients with moderate vs 6 patients with severe allergic reactions). An earlier Dutch study ($n = 173$) obtained comparable results in children and found a significant difference in IgE levels against cashew nut extract and against Ana o 3 between the tolerant and cashew nut allergic group ($p < .001$), and no significant difference in both IgE levels between patients with mild symptoms and anaphylaxis ($p = .916$).⁷

In conclusion, this study showed that IgE against Ana o 3 is a very good predictor of cashew nut allergy in adults, correctly categorizing 72% of patients as allergic or tolerant in our study population. Although an association with symptom severity was observed, IgE against Ana o 3 and against cashew nut extract were not able to predict severity of cashew nut allergy.

AUTHOR CONTRIBUTIONS

All authors have made substantial contributions to conception and design of this study and have been involved in drafting or revising the manuscript. All authors have given final approval of the version to be published and agreed to be accountable for all aspects of the work. E. Kallen had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

KEYWORDS

Ana o 3, cashew nut allergy, cashew nut extract, diagnostic value, severity

CONFLICT OF INTEREST STATEMENT

Emily Kallen, Juliette Bollemeijer and André Knulst have nothing to disclose. Anna Ehlers has received research support from EUROIMMUN. Paco Welsing has nothing to disclose. Ronald van Ree has stock options in Angany Inc; is a consultant and/or speaker for HAL Allergy, Citeq BV, Angany Inc., Reacta Healthcare Ltd., Mission MightyMe, AB Enzymes, ALK and Thermo Fisher Scientific. Thuy-My Le is a speaker for and/or received research support from Novartis, Thermo Fisher Scientific and AbbVie.


DATA AVAILABILITY STATEMENT


The data that support the findings of this study are available from the corresponding author upon reasonable request.

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