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Phenotypical characterization of peanut allergic children with differences in cross-allergy to tree nuts and other legumes

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Running title: Peanut allergic phenotypes in pediatrics

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PAI

Abstract

Background. Peanut allergy in children is often associated with allergies to tree nuts and/or legumes. The aim of the present study was to analyze in cluster a cohort of children allergic to peanuts and assessed for cross-reactivity to nuts and legumes and to identify different phenotypes.

Methods. We included retrospectively 317 children with peanut allergy evaluated at the Allergy Unit of the Saint Vincent Hospital of Lille in the last 12 years. A complete work-up for peanut allergy and nuts and legumes was carried out for each patient. A hierarchical agglomerative clustering method was used to search for clusters of individuals in the evaluated cohort.

Results. Cross-allergy to TN and/or other legumes was identified in 137 patients (43.2%), atopic dermatitis being a major risk factor (adjusted OR = 16 [95%CI: 7.4-37]; $p < 0.001$). Three phenotypes emerged from cluster analysis. Cluster 1 (72 patients) is characterized by high level of rAra h 2, low threshold reactive doses for peanut and high proportion of asthma; Cluster 2 (93 patients) is characterized by high threshold reactive doses for peanut and the lowest proportion of cross-allergy to TN and/or legumes; Cluster 3 (152 patients) has a high risk of cross-allergy to TN and/or legumes and most patients suffer from eczema.

Conclusions. The three phenotypes highlighted by the present study could be useful to identify children with high risk of cross-allergic reaction to TNs and legumes early after PA diagnosis.

Registration. This study has been registered on clinicaltrials.gov under the number NCT02961452.

Key Words: Children, cluster analysis, cross-allergy, legumes, peanut allergy, tree nuts.

Introduction

Peanut allergy (PA) – a widely studied allergy in the pediatric population with an estimated prevalence of 1.3% in Europe (1) – and tree nut (TN) allergy – with a prevalence ranging from 0.05 to 4.9 % (2) – are clinically similar conditions, often coexisting (3) even though peanuts do not belong to the TN family, but to the legumes one. Children suffering from these allergy often experience an impaired health-related quality of life (HRQL), as they caregivers might do as well (4). In facts, these allergies are quite complexes : TN allergy is a long-lasting condition, with fatal reactions being reported for nearly all TNs (3,5,6). When evaluating a patient with a suspected food allergy, many parameters need to be considered, including the clinical background and history, and the type of symptoms possibly elicited by the food and cross reactions to other allergens.

Legumes and TNs contain seed storage protein which are orthologs of peanut globulins (rAra h1, rAra h 3) and 2S albumins (rAra h 2), and that may possibly provoke allergic reactions (7,8), but

cross-reactivity between peanuts and TN and other legumes may also result from primary sensitization in PA patients (9). Because of potential IgE-binding cross-reactions, clinicians might advise PA children to avoid eating new TNs and other legumes. Nevertheless, to distinguish sensitization from allergy, the only gold standard remains the oral food challenge (OFC), possibly a double-blind placebo-controlled food challenge (DBPCFC), which also allow to assess the threshold dose to which patients react and the severity of clinical symptoms (10).

Considering the relatively high prevalence of PA, the assessment of cross-allergy to every single allergenic TN and legume requiring a full allergy work-up may therefore take even a few years to be completed. Even though rates of cross-allergy to TN have been reported to range from 28% to 50% in PA (11–14), very few studies have characterized these cross-allergic patients. Therefore, targeting patients with severe or cross-allergic phenotypes would be highly useful for allergists when determining appropriate management and follow-up practices for PA patients.

The aim of the present study was to analyze in cluster a cohort of children allergic to peanuts and to identify possible different phenotypes. This statistical approach has not been previously used to identify cross-allergic phenotypes. We also tried to describe cross-allergy patterns in PA children and to identify possible risk factors for cross-allergy to TN and legumes.

Methods

Patients included

We conducted a retrospective study including all children suffering from PA who had a complete work-up for cross-allergy to TN and other legumes, performed at the Allergy Unit of the Saint Vincent Hospital of Lille (France) from March 2004 to May 2016.

PA was defined by clinical history, positive skin prick test (SPT) to peanut, positive sIgE levels for a major peanut component – rAra h 1, or rAra h 2, or rAra h 3 (>0.1 kUA/l, ImmunoCAP®, Thermo Fisher Scientific) – and a positive DBPCFC.

We excluded all patients who had an incomplete evaluation for major peanut components at the time of their DBPCFC to peanut, and those who refused the food challenge.

Data collection at inclusion and variables used for cluster analysis

Age at peanut DBPCFC and sex were recorded for each patient. We systematically looked for a previous diagnosis of atopic dermatitis (AD), asthma, and allergic rhinitis (AR). These diagnoses were made by the children's physician and recorded in the personal medical chart of each patient.

Sensitization to TN and/or legumes was defined by the positivity of SPT and serum specific IgEs for a food allergen.

The diagnosis of "food allergies other than TN or legumes" was based on a clinical history suggestive of IgE-mediated food allergy, positive SPT and serum IgEs, and/or positive OFC. We analyzed the results of each patient's first DBPCFC to peanut (threshold reactive dose and symptoms score) together with the results of blood tests (sIgE for major peanut components rAra h 1, rAra h 2, and rAra h 3) (ImmunoCAP®, Thermo Fisher Scientific). For the cluster analysis, we recorded the threshold reactive dose in mg of peanut protein (PP) as a variable, but did not use the Astier's symptom score (15), being not recommended in current guidelines (16).

Assessing cross-allergy to tree nuts and other legumes

EAACI guidelines for the diagnosis of food allergy (17) were applied to search for cross-allergies. For each child, a cross-allergy diagnosis (positive or negative) was determined for each individual TN and legume.

Cross-allergy to TNs and/or other legumes was diagnosed only if the patient had at least a convincing clinical history of significant type I allergic reaction after isolated ingestion of the individual food in the preceding six months, with a positive SPT and a positive IgE assay to the individual food (> 0.1 kUA/l, ImmunoCAP®, Thermo Fisher Scientific) and/or a positive OFC for that specific food. Some patients underwent DBPCFC to diagnose allergy to TNs and legumes allergy, but, in most cases, a single-blinded OFC was performed.

Skin prick tests

The prick-to-prick technique was performed with native extract produced by crushing and mixing (1:10 wt/vol phosphate buffered saline) fresh (raw) natural food (18). SPTs were considered positive when the largest wheal diameter was 3 mm or greater and at least 50% greater than the positive controls (10 mg/mL histamine dihydrochloride and codeine phosphate) (ALK-Albello, France) (19).

To assess cross-reactivity to peanut, the following foods were systematically tested: cashew, pistachio, almond, hazelnut, pine nut, walnut, pecan, Brazil nut, and Macadamia nut, to look for TN allergies; and lentil, soya, chickpea, pea, white bean, broad bean, and lupine flour, to look for legumes allergies.

OFC

Single-blinded OFCs and DBPCFCs were performed and results recorded in compliance with international guidelines (20). OFC were performed under strict hospital surveillance at least four weeks after the last patient's reaction. Patients had not been taking any H1-antihistamines or other drug possibly affecting the results of the test. A physician trained in allergy was present for each challenge. Symptoms were scored according to Astier et al. (15). Natural food extracts mixed with boiled apples or mashed potatoes as a matrix were given in gradually increasing doses in 11 sequential 20 min steps. The doses of extract were increased as follows: 1 mg, 5 mg, 10 mg, 50 mg, 200 mg, 400 mg, 600 mg, 900 mg, 1500 mg, 3000 mg, and 5000 mg. For the DBPCFC to peanut, whole crushed roasted peanuts were used and the reactive cumulated dose was expressed in mg of PP equivalent, corresponding to 0.25 mg to 2941.5 mg of PP (21).

Ethical considerations

The study was reviewed and approved by our institutional review board, and all patients and their parents were given written information about the study. Written consent was obtained before each food challenge after informing the children and at least one of the parents.

Registration

This study has been registered on clinicaltrials.gov under the number NCT02961452.

Statistical methods

Risk factors were evaluated with univariate odds ratios and their 95% confidence intervals. A logistic regression was conducted to identify risk factors adjusted to covariates. As the logistic regression is unstable in the present situation (all allergic patients are sensitized), we conducted the multivariate analysis only on sensitized patients to TN and/or other legumes. A hierarchical agglomerative clustering method was used to search for clusters of individuals in the population (22). This “bottom-up” approach begins with each observation in its own cluster and then merges these clusters into successively larger clusters. The algorithm needs to define the distance between two observations to evaluate a dissimilarity matrix. Because the variables were categorical and quantitative, the Gower distance was used (22). A variable standardization was applied to give the same weight to all variables in the analysis. Ward linkage, which minimizes the within-cluster sum of the square, was applied. The resulting dendrogram was used to find the optimal number of clusters. For cluster analysis, threshold reactive dose was discretized in four groups, according to its quartiles. For categorical variables, differences between groups were evaluated using Khi-2 test or Fisher exact test as appropriate. For continuous variables, Wilcoxon test was used for the comparison of two medians and Kruskal-Wallis test for the comparison of more than two medians. All statistical tests were 2-sided, and a p value ≤ 0.05 was regarded as statistically significant. Statistical analysis was performed with R 3.2.5.

Results

Patients' characteristics, cross-allergy and cross-sensitization

After evaluating patients as for inclusion and exclusion criteria, 317 patients were included in the study. Most patients were male (62.8%). Mean age ($\pm$ SD) was 7 ± 3.9 years. AD was observed in 67.5% of patients, asthma in 64.7%, and sensitization to one or more TN and/or other legume in

87.1% (n=276 patients). The characteristics of our cohort are shown in Table 1. At least one cross-allergy to TNs and/or legumes other than peanut was identified in 137 patients (43.2%), documented with a positive OFC in 115 of them (84%). In the group of the 137 cross-allergic patients, 82 (59.9%) were male, 128 (93.4%) had AD, 101 (73.7%) had asthma, 93 (67.9%) had asthma and AD, and 52 (38%) had a food allergy other than TN or other legumes. The mean threshold dose for DBPCFC to peanut ($\pm$ SD) was 211.4 $\pm$ 418.8 mg PP. The only risk factor for cross-allergy to TN and/or other legumes identified with multivariate analysis was AD (adjusted OR = 16 [95%CI: 7.4-37]; p <0.001).

Cross-allergy to TN and legumes affected patients with the following frequencies: at least one TN 38.8% at least one TN; 7.9% at least one legume; 21.8% hazelnut; 17.7% cashew; 17.3% pistachio; 3.8% walnut; 3.2% pea; 2.8% lentil; 2.2% almond; 1.9% soya; 0.9% lupine flour; 0.6% chickpea; 0.6% pecan nut. No cross-allergy to pine nut or other nuts (Brazil, macadamia) nor to beans was found (Figure 1 and 2).

Cluster analysis-defined PA phenotypes

Hierarchical classification of the main variables produced three independent clusters (Table 1).

Cluster 1, “*Severe PA with high rAra h 2 levels*” (72 subjects), was mainly composed by girls (55.6%), presenting with the highest proportion of asthma (80.6%) and AR (90.3%), the lowest threshold reactive doses in DBPCFC to peanut (median (percentile 25°-75°): 41.5 (25.55-67.05) mg PP), and moderate proportion of patients with cross-allergy to TNs and/or other legumes (31.9%). Cluster 1 was characterized by highest mean level of rAra h 2 (81.3kUA/l), rAra h 1 (62.3 kUA/l), and rAra h 3 (33.7 kUA/l).

Cluster 2, “*Mild PA without cross-allergy to TN and/or other legumes*” (93 subjects), was

associated with the highest proportion of boys (72%), the lowest proportion of asthma (35.5%) and AD (32.3%), the highest threshold reactive doses in DBPCFC to peanut (median (percentile 25°-75°): 191.5 (41.5-341.5) mg PP), lower symptom score (70% of patients with grade I or II), and the lowest proportion of patients with cross-allergy to TNs and/or other legumes (1.1%).

Cluster 3, *“PA with AD and frequent cross-allergy to TN and/or other legumes”* (152 subjects), was characterized by the highest proportion of AD (94.7%), the highest proportion of allergic multimorbidity (other food allergy (40.8%), AD and asthma (69.7%)), low to mild threshold reactive doses in DBPCFC to peanut (median (percentile 25°-75°): 91.5 (63.4-341.5) mg PP), the lowest mean level of rAra h 2 (14.2 kUA), and the highest proportion of patients with cross-allergy to TNs and/or other legumes (74.3%).

Discussion

Three distinct phenotypes of PA were identified through clinical main characteristics of children. PA patients that may be qualified as severe considering a low threshold of reaction to peanut (Cluster 1), were mainly girls. Such association between a severe phenotype and a gender prevalence has already been reported by other Authors (23). In this group, we highlighted an correlation between low PP thresholds and high levels of rAra h 1, rAra h 2 and rAra h 3 with a, as described in literature (24,25). Also, as for Cluster 1 phenotype, most children suffered from asthma (80.6%), which is a known risk factor for anaphylaxis (26). Patients belonging to Cluster 2 presented high PP thresholds and they very rarely suffered from cross-allergies. Very interestingly, children presenting with AD suffered from cross-allergies to TN and/or legumes, which is a very important finding from a clinical point of view.

In our study, AD was identified as the leading risk factor for cross-allergy in PA children in general, and not only in patients belonging to the Cluster 3 phenotype. This strong association is concordant

with the results of a recent meta-analysis showing that AD, as a comorbidity of multiple food allergies, precedes the development of food sensitization and allergy, with a possible causal relationship (27). Immunologically, it could be speculated that these children, with a skin barrier defect, were cutaneously exposed to several TN and/or legumes early in their lives and developed sensitizations and then allergies to these foods. Even though it would be interesting to know the ethnicity and the dietary habits of these patients' families, especially as for children from Cluster 3, we lacked such information in the present retrospective study.

Patients belonging to Cluster 3, might also suffer from a deeply impaired HRQL, since AD is already known to be a risk factor for a reduced quality of life in children and parents. Nevertheless, they also suffer from multiple food allergies which might therefore worsen their HRQL (11).

It is therefore crucial to reach a prompt and complete diagnosis in PA patients. Therefore, in allergy centers, it is important to diagnose, treat and support children through a multidisciplinary team, involving allergists, dermatologists, pediatric pulmonologists, psychologists and dieticians.

In our center, we tend to assess cross-allergy in all PA patients, but Authors do not seem to globally agree on this precise topic (28,29). In our cohort, the most common TN allergy was related to hazelnut (21.8%), in line with other epidemiological studies (3). A quite interesting result of our study would concern the diagnosis of cross-reactivity between walnut and pecan: we highlighted cross-allergy in 12 walnut allergic patients but only in two children with a diagnosis of pecan allergy. As in other previous studies, we confirmed cross-reactivity between cashew and pistachio (11). Also, we need to underline that we did not find any case of cross-allergy to Brazil nut nor Macadamia nut, probably because these TNs are expensive and not widely consumed in our area.

An uncommon aspect of our results is the high frequency of AR (76.3%), if compared with other French cohorts (23), but such datum is probably related to a recruitment bias since our study was conducted in northern France, an endemic area for birch allergy. A possible limitation of the study is

that we didn't include in our analysis the evaluation of Ara h 8 and Ara h 9 (PR-10 and LTP), which could actually have a very interesting impact on the creation of clusters. This is due to the fact that in the present retrospective study we were missing this information for most patients.

To our knowledge, the cohort of PA children reported in the present paper is the largest with a diagnosis of clinically significant cross-allergy to TNs and/or other legumes. The phenotypical approach proposed by our study, should help clinicians to easily identify the different groups of PA patients and to personalize their management. Allergists should:

- associate severe forms of peanut allergy with asthma and take it into account when prescribing emergency kits;
- remember that forms with high threshold are rarely associated with cross-reactivity to TN and/or legumes;
- be very careful when assessing patients suffering from AD, since they most likely will present multiple food allergies.
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References

1. Nwaru BI, Hickstein L, Panesar SS, et al. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. *Allergy* 2014; 69: 992-1007.
2. McWilliam V, Koplin J, Lodge C, et al. The Prevalence of Tree Nut Allergy: A Systematic Review. *Curr Allergy Asthma Rep* 2015; 15: 54.
3. Sicherer SH, Furlong TJ, Muñoz-Furlong A, et al. A voluntary registry for peanut and tree nut allergy: characteristics of the first 5149 registrants. *J Allergy Clin Immunol* 2001; 108: 128-132.

- Accepted Article
4. Antolín-Amérigo D, Manso L, Caminati M, et al. Quality of life in patients with food allergy. *Clin Mol Allergy* 2016; 14: 4.
 5. Clark AT, Ewan PW. Interpretation of tests for nut allergy in one thousand patients, in relation to allergy or tolerance. *Clin Exp Allergy* 2003; 33: 1041-1045.
 6. Pumphrey RS. Lessons for management of anaphylaxis from a study of fatal reactions. *Clin Exp Allergy* 2000; 30: 1144-1150.
 7. Teuber SS, Beyer K. Peanut, tree nut and seed allergies. *Curr Opin Allergy Clin Immunol* 2004; 4: 201-203.
 8. van Ree R. Clinical importance of cross-reactivity in food allergy. *Curr Opin Allergy Clin Immunol* 2004; 4: 235-240.
 9. Aalberse RC. Assessment of allergen cross-reactivity. *Clin Mol Allergy* 2007; 5: 2.
 10. Bock SA, Sampson HA, Atkins FM, et al. Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: a manual. *J Allergy Clin Immunol* 1988; 82: 986-997.
 11. Maloney JM, Rudengren M, Ahlstedt S, et al. The use of serum-specific IgE measurements for the diagnosis of peanut, tree nut, and seed allergy. *J Allergy Clin Immunol* 2008; 122: 145-151.
 12. Sicherer SH, Burks AW, Sampson HA. Clinical features of acute allergic reactions to peanut and tree nuts in children. *Pediatrics* 1998; 102: e6.
 13. Ewan PW. Clinical study of peanut and nut allergy in 62 consecutive patients: new features and associations. *BMJ* 1996; 312: 1074-1078.
 14. Hourihane JO, Roberts SA, Warner JO. Resolution of peanut allergy: case-control study. *BMJ* 1998; 316: 1271-1275.

- Accepted Article
15. Astier C, Morisset M, Roitel O, et al. Predictive value of skin prick tests using recombinant allergens for diagnosis of peanut allergy. *J Allergy Clin Immunol* 2006; 118: 250-256.
 16. Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology, European Academy of Allergy and Clinical Immunology, PRACTALL consensus report. *J Allergy Clin Immunol* 2012; 130: 1260-1274.
 17. Muraro A, Werfel T, Hoffmann-Sommergruber K, et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. *Allergy* 2014; 69: 1008-1025.
 18. Bruijnzeel-Koomen C, Ortolani C, Aas K, et al. Adverse reactions to food. European Academy of Allergology and Clinical Immunology Subcommittee. *Allergy* 1995; 50: 623-635.
 19. Sampson HA. Food allergy. Part 2: diagnosis and management. *J Allergy Clin Immunol* 1999; 103: 981-989.
 20. Bindslev-Jensen C, Ballmer-Weber BK, Bengtsson U, et al. Standardization of food challenges in patients with immediate reactions to foods--position paper from the European Academy of Allergology and Clinical Immunology. *Allergy* 2004; 59: 690-697.
 21. Souci SW, Fachmann W, Kraut H, et al. Food composition and nutrition tables. Stuttgart: Medpharm Scientific Publishers 2008.
 22. Kaufman L, Rousseeuw PJ. Finding Groups in Data: An Introduction to Cluster Analysis. New York: Wiley 1990.
 23. Just J, Elegbede CF, Deschildre A, et al. Three peanut-allergic/sensitized phenotypes with gender difference. *Clin Exp Allergy* 2016; 46: 1596-1604.
 24. Zee T van der, Dubois A, Kerkhof M, et al. The eliciting dose of peanut in double-blind, placebo-controlled food challenges decreases with increasing age and specific IgE level in

children and young adults. J Allergy Clin Immunol 2011; 128: 1031-1036.

25. Blumchen K, Beder A, Beschorner J, et al. Modified oral food challenge used with sensitization biomarkers provides more real-life clinical thresholds for peanut allergy. J Allergy Clin Immunol 2014; 134: 390-398.
26. Järvinen KM, Sicherer SH, Sampson HA, et al. Use of multiple doses of epinephrine in food-induced anaphylaxis in children. J Allergy Clin Immunol 2008; 122: 133-138.
27. Tsakok T, Marrs T, Mohsin M, et al. Does atopic dermatitis cause food allergy? A systematic review. J Allergy Clin Immunol 2016; 137: 1071-1078.
28. Ewan PW, Clark AT. Long-term prospective observational study of patients with peanut and nut allergy after participation in a management plan. Lancet Lond Engl 2001; 357: 111-115.
29. Du Toit G, Lack G. Optimizing the diagnosis of peanut and tree nut allergy. Clin Exp Allergy 2003; 33: 1019-1022.

Table 1- Characteristic features of patients according to cluster analysis (N=317)

		Total cohort n = 317	Cluster 1 n = 72	Cluster 2 n = 93	Cluster 3 n = 152	P-value**
Gender (male), n (%)*		199 (62.8%)	32 (44.4%)	67 (72%)	100 (65.8%)	0.00076
Age at DBPCFC to peanut*	mean (sd)	7 (3.9)	7.7 (3.6)	7.5 (4.3)	6.5 (3.7)	0.024
	median (25°-75°)	6 (4-9)	7 (5-10)	6 (4-9)	5 (4-9)	
Asthma. n (%)*		205 (64.7%)	58 (80.6%)	33 (35.5%)	114 (75%)	<0.0001
Atopic dermatitis (AD), n (%)*		214 (67.5%)	40 (55.6%)	30 (32.3%)	144 (94.7%)	<0.0001
Allergic rhinitis (AR), n (%)*		242 (76.3%)	65 (90.3%)	49 (52.7%)	128 (84.2%)	<0.0001
Other food allergy than peanut or other legumes, n (%)*		88 (27.8%)	13 (18.1%)	13 (14%)	62 (40.8%)	<0.0001
AD + Asthma		152 (47.9%)	35 (48.6%)	11 (11.8%)	106 (69.7%)	<0.0001
Sensitization to tree nuts and/or other legumes, n (%)*		276 (87.1%)	65 (90.3%)	63 (67.7%)	148 (97.4%)	<0.0001
Cross-allergy to tree nuts and/or other legumes, n (%)*		137 (43.2%)	23 (31.9%)	1 (1.1%)	113 (74.3%)	<0.0001
Threshold dose*o	mean (sd)	242.7 ± 447.7	64.5 ± 83.3	321.7 ± 533.2	276.6 ± 472.6	<0.0001
	median (25°-75°)	91.5 (41.5- 191.5)	41.5 (25.55- 67.05)	191.5 (41.5- 341.5)	91.5 (63.4- 341.5)	
rAra h 1*	mean (sd)	19 ± 31.6	62.3 ± 36.1	5.7 ± 13.1	6.5 ± 14.7	<0.0001
	median (25°-75°)	1.5 (0.1-21)	63.5 (29.9- 100)	0.3 (0.1-4.5)	0.2 (0.1-4.4)	
rAra h 2*	mean (sd)	31 ± 36.5	81.3 ± 27.9	14.2 ± 20.1	17.4 ± 24.8	<0.0001
	median (25°-75°)	13.2 (2.4-50.6)	100 (68.4- 100)	5.7 (1.4-19)	5.6 (1.7-21.8)	
rAra h 3*	mean (sd)	8.7 ± 21.6	33.7 ± 34.9	1.5 ± 3.9	1.4 ± 3.3	<0.0001

	median (25°-75°)	0.3 (0.1-3.1)	25.9 (2.4-52.1)	0.1 (0.1-0.7)	0.1 (0.1-0.8)	
Symptom's Score^{°°}	1	72 (22.7%)	8 (11.1%)	31 (33.3%)	33 (21.7%)	0.033
	2	124 (39.1%)	32 (44.4%)	34 (36.6%)	58 (38.2%)	
	3	94 (29.7%)	27 (37.5%)	22 (23.7%)	45 (29.6%)	
	4	27 (8.5%)	5 (6.9%)	6 (6.5%)	16 (10.5%)	

*Variables considered for cluster analysis. Threshold dose was discretized in 4 groups by quartiles in the cluster analysis.

** For categorical variables, Khi-2 (χ^2) test when conditions were respected, Fisher exact test otherwise. For continuous variables, Kruskal-Wallis test. Bold typed text indicates statistical significance. No multiplicity correction has been used.

° The reactive cumulated dose in DBPCFC to peanut expressed in mg of peanut protein equivalent.

°°Symptom score in DBPCFC to peanut according to Astier et al (15).

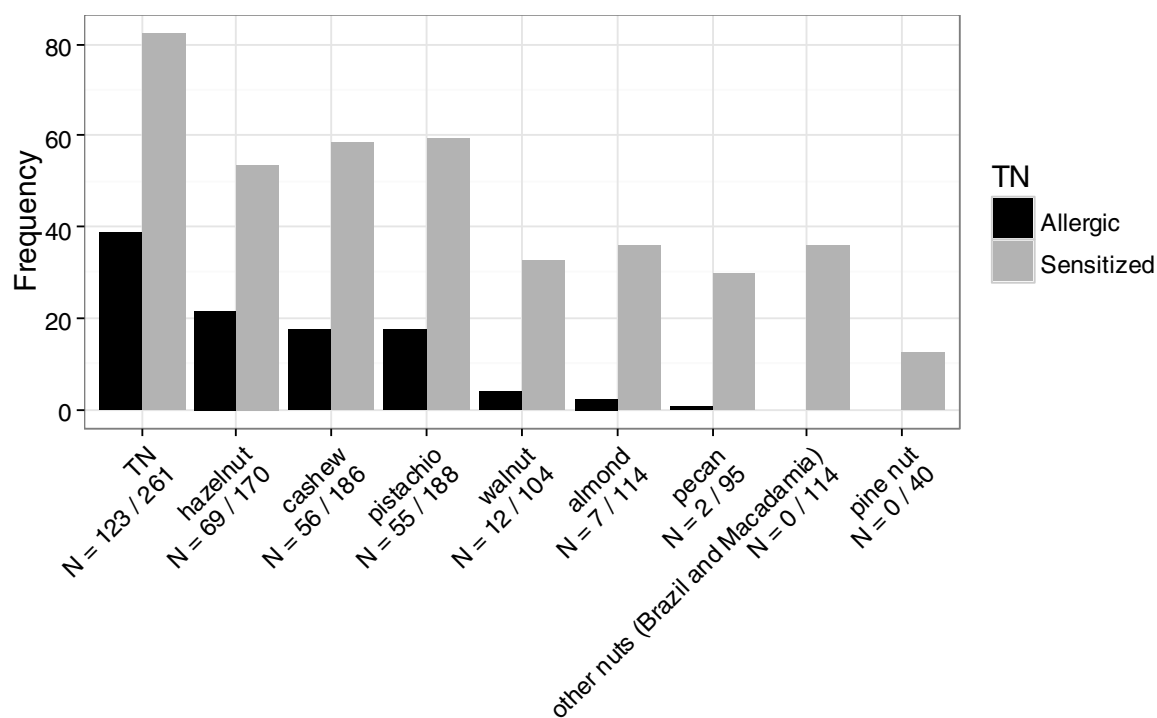


Figure 1 - Tree nut (TN) allergy and sensitization rates in our cohort (N =317).
Allergens are displayed with the number of allergic / the number of sensitized patients.
Frequency is expressed in % of patients.

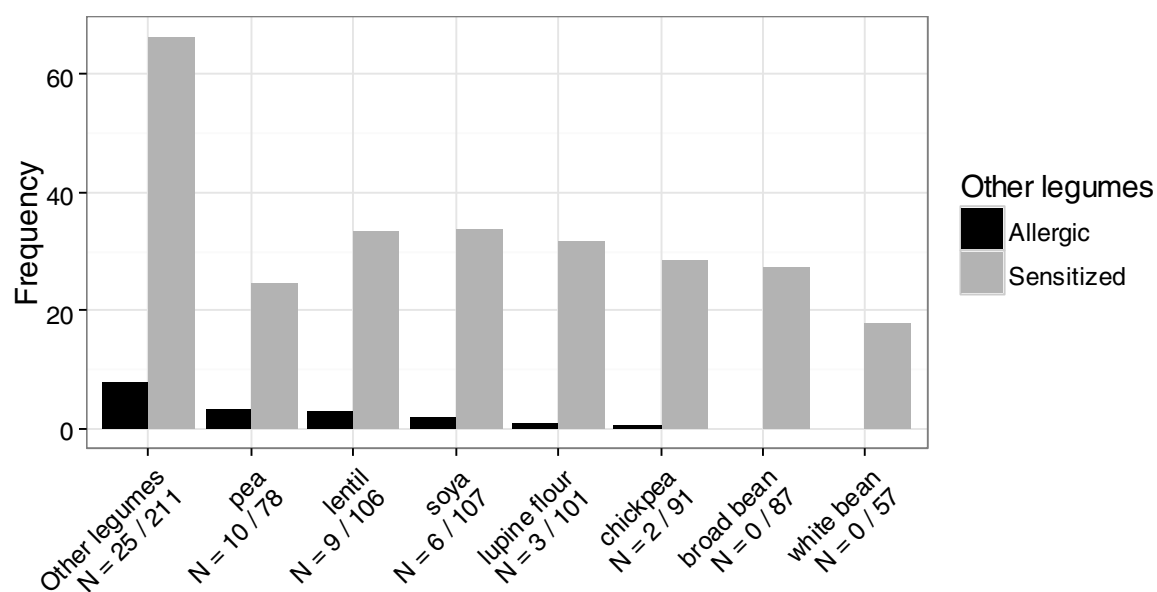


Figure 2 - Legumes allergy and sensitization rates in our cohort (N = 317).

Allergens are displayed with the number of allergic / the number of sensitized patients.

Frequency is expressed in % of patients.