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Three peanut allergic/sensitized phenotypes with gender difference

7 words

Short title: peanut allergic/sensitized phenotypes

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Contributors

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Abstract 293 (300)

Background: Peanut allergic reactions are heterogeneous ranging from mild symptoms to anaphylaxis. **Objective:** Identify peanut allergic/sensitized phenotypes to personalize patient management. **Methods:** A combined factor and cluster analysis was used to study the phenotypes of 696 patients diagnosed with peanut sensitization and enrolled in the MIRABEL survey. The method was first applied to the 247 patients with an Oral Food Challenge (OFC). It was then applied to the 449 patients without OFC to confirm the findings in an independent population. **Results:** Three independent clusters emerged from the OFC subgroup. Cluster 1, "*Severe peanut allergy with little allergic multimorbidity"* (123 subjects), had the highest proportion of patients with positive OFC (92%), a medium level of peanut protein inducing a positive OFC (235 mg), lower percentage of allergic multimorbidity (2% asthma plus atopic dermatitis (A+AD), no cases of A+AD + multiple food allergies (MFA)). Cluster 2, "*Severe peanut allergy with frequent allergic multimorbidity"* (62 subjects), had a high proportion of patients with positive OFC (85%) with the lowest level of peanut protein inducing a positive OFC (112mg), 89% allergic subjects, 100% with allergic multimorbidity (A+AD) and 84% with A+AD+MFA. Cluster 3, "*Mild peanut* allergic/sensitized *phenotype"* (62 subjects), had the lowest mean age, the lowest proportion of patients with positive OFC (53%) with a high level of peanut protein inducing a positive OFC (770 mg), a low percentage of allergic multimorbidity (48% A+AD+MFA). The two severe peanut allergy phenotypes were more frequent in girls. The same clusters were found in the subgroup of patients without OFC. **Conclusion & Clinical Relevance:** Besides the classic markers associated with lower threshold doses of OFC (such as SPT and rAra h2), allergic multimorbidity and female gender should also be taken into account to better adapt the progressive dosage of provocation tests.

Key words: asthma, atopic dermatitis, cluster analysis, gender, peanut allergy, multimorbidity.

Abbreviations

Specific immunoglobulin E: sIgE

Skin prick test: SPT

Atopic dermatitis: AD

Asthma: A

Allergic rhinitis: AR

Multiple Food Allergies: MFA

Oral food challenge: OFC

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Introduction

Peanut allergy is a common food allergy affecting up to 1.3% of children in Europe[1]. Its prevalence is on the increase and this is reflected in an increased prevalence of hospitalization for peanut-induced anaphylaxis in the United States[2]. However, the severity of systemic allergic reactions to peanut is variable and fatal peanut-induced anaphylaxis is rare[3]. Moreover, a considerable number of children with positive specific immunoglobulin E (sIgE) and positive skin prick test (SPT) are asymptomatic or present a milder clinical picture[4,5,6,7]. Thus, it is crucial to better detect patients with a severe food allergy phenotype for appropriate follow-up care and management.

The diagnosis of peanut allergy in comparison to peanut sensitization is not always easy. The most relevant features to diagnose peanut allergy would appear to be clinical in real life or in provocation tests. Moreover, a small proportion of children with peanut allergy can outgrow their allergy[8]. On the other hand, the severity of the disease can also increase over time. This is illustrated by contradictory results in studies, some of which have previously suggested a relationship between a history of anaphylaxis or severe symptoms and the risk of anaphylaxis upon subsequent exposure and others the opposite[9,10,11].

Nicolaou et al.[12] found a high rate of false-positive SPT and irrelevant sIgE results for peanut. The threshold level of peanut sIgE or SPT to predict a positive provocation test is unclear[1314]. These discrepancies in the current approach to peanut allergy testing could be improved by component-resolved diagnosis which has been extensively explored in this area. In 2004, Koppelman et al.[15] first suggested the importance of the peanut component rAra h 2 in predicting reactivity or tolerance to peanut. More recently, other components of peanut such as rAra h 6, have been found to be associated with the risk of anaphylaxis[16]. However, to date, a provocation test remains necessary not only to confirm diagnosis but also to assess the severity of peanut allergy (related to the threshold reactive dose).

These features underline the necessity to perform provocation tests to distinguish between peanut sensitized and allergic patients, but this test is at risk of anaphylaxis and time consuming.

A novel approach to distinguish patients who present peanut allergic or sensitized phenotypes with different clinical and biological characteristics, is to identify different disease phenotypes by cluster analysis. This statistical approach has never been performed to identify allergic/sensitized phenotypes.

The MIRABEL survey is a multicentre survey based on the voluntary participation of peanut-allergic/sensitized patients from Metropolitan France, Belgium and Luxembourg to evaluate the allergic risk in patients with well-characterized peanut allergy or sensitization [17]. It is thus an ideal cohort in which to test the hypothesis that peanut allergic/sensitized phenotypes exist.

We set out to define allergic/sensitized phenotypes by unsupervised analysis in a subgroup of patients of the MIRABEL survey who had undergone oral food challenges (OFC) taking into account informative parameters such as clinical symptoms, SPT, sIgE to native and informative epitopes (rAra h 2). To generalize these phenotypes to the entire allergic population, the same analysis was performed in an independent population of patients without OFC.

Material and Methods

MIRABEL design and inclusion of patients

Between April 2012 and December 2013, allergists were asked to include consecutive patients with suspected peanut allergy. Patients were then classified as "sensitized" on the basis of positive SPT performed with commercial extracts (mean wheal diameter ≥ 3 mm) and sIgE to rAra h 2 (≥0.35 kUA/L; ImmunoCAP, Thermofisher, Sweden)[18] without any clinical reaction, or "allergic" based on sensitization (as previously defined) with an allergic reaction to peanut exposure.

Ethics

The study was approved by the French Data Protection Authority (CNIL) (Authorization no. DE-2011-048). All patients or parents signed an informed consent.

Medical questionnaire and oral food challenge

Data were collected by a questionnaire filled in by the allergist after medical diagnosis of peanut allergy and included the following variables (as previously published[19]). Briefly:

The age at diagnosis of peanut allergy.

Symptom severity during real-life exposure was classified into two categories: *mild to moderate reactions* (urticaria or angioedema without respiratory symptoms, rash/dermatitis, isolated and mild to moderate gastro intestinal symptoms); or *severe reactions* (anaphylactic shock, laryngeal angioedema, acute asthma, systemic serious reaction (involving two or more organs)[20].

Active allergic comorbidities over the past year, including asthma (A), atopic dermatitis (AD), allergic rhinitis (AR) and multiple food allergies (MFA) were diagnosed by an experienced allergist from the patient's medical records.

SPT were performed using different peanut and food extracts (mainly from Stallergènes, Antony, France). As the MIRABEL survey is observational, the patients were administered the OFC according to the physician's practice either by a single-blind or double-blind placebo-controlled challenge or as an open OFC. For positive OFCs, the reactive cumulated dose, based on objective symptoms only, was expressed in mg of peanut protein equivalent. The OFC was considered negative in the absence of an objective sign for a cumulative dose ≥ 7 g of peanut.

Dietary advice provided by the allergist was recorded as: "strict eviction " if the patient was advised to avoid all products containing peanuts and products with PAL; compared with a combined category of "lax" if the patient was merely advised to avoid products containing peanuts but that PAL products were allowed; and "absent" if the patient was advised that no avoidance was necessary.

Variable selection for cluster analysis

The variables for statistical analysis were those that reflected physiologic parameters (age at diagnosis and age at time of OFC, gender) and those related to the clinical presentation of peanut allergy such as the allergic/sensitized status, route of exposure that induced reaction (ingestion and/or inhalation and/or contact), the test results (SPT, rAra h 2, OFC) and allergic comorbidities. In case of two highly correlated variables, only the one considered as the most relevant was retained in the analysis. The variables selected for analysis are marked in Table 1

by a ‡. Composite variables were used to distinguish patients with one, two or three multimorbidity symptoms: one variable for patients with both A and AD (A+AD), and one for patients with both A+AD and MFA (A+AD+MFA).

Variable reduction and cluster analysis

Phenotype clusters were identified by coupling a factor analysis with a cluster analysis as previously reported by Just et al .[19]. A factor analysis for mixed data (categorical and continuous) was first applied to the selected variables to study their associations and identify which variables contributed the most to explaining the variability of the dataset[21]. Factor analysis also makes it possible to reduce the dimension of the dataset to a few principal components. A hierarchical cluster analysis was then applied to these principal components to classify the population into homogeneous groups of peanut allergy severity. The method is based on Ward's minimum variance criterion which minimizes the total within-cluster variance. The distance between individuals was calculated using the Euclidian distance. Thus, variables between the different groups were compared using the one-way ANOVA test for continuous variables and the Chi-squared test for categorical variables. The Kruskal-Wallis and the Fisher’s exact tests were respectively used when the required conditions were not respected to perform the ANOVA and the Chi-squared tests. Statistical analyses were performed with the FactoMineR package of R version 3.1.1.

Results

Description of the population

785 patients were recruited by 70 allergists. Complete information was available for 696 patients, and 247 of these had complete OFC results. The variables have been fully described in a previous article about the MIRABEL survey[17].

Variable associations

Factor analysis applied to the OFC subgroup using all selected variables resulted in three principal components explaining 46% of the total variance. The first component was composed of allergic multimorbidity variables. The second component was composed of the age at which the OFC was conducted and the time between diagnosis and the OFC. The third component included SPT, sIgE to rAra h 2 and OFC results. A similar structure was obtained when applying factor analysis to the population without OFC, except that the allergic/sensitized status was also part of the second component and associated with age at diagnosis.

Peanut allergic/sensitized phenotypes of the 247 patients with OFC

Three independent clusters emerged from the application of a hierarchical classification on the three principal components selected from the previous factor analysis.

Cluster 1, "*Severe peanut allergy with little allergic multimorbidity"* (123 subjects), had the highest proportion of patients with positive OFC (92%), the highest proportion of severe reactions upon exposure via ingestion (84%),a medium level of peanut protein equivalent inducing a positive OFC (235 mg) associated with a high mean level of rAra h 2 (34kUA/l), and finally a lower percentage of allergic multimorbidity (2% asthma plus atopic dermatitis (A+AD), no cases of A+AD + MFA) (Table 1).

Cluster 2, "*Severe peanut allergy with frequent allergic multimorbidity"* (62 subjects), had a

high proportion of patients with positive OFC (85%) with the lowest level of peanut protein inducing a positive OFC (112mg) associated with the highest mean level of SPT wheal size (13mm), the highest mean level of rAra h 2 (43 kUA/l) and the highest proportion of severe reactions upon exposure via inhalation. This cluster was characterized by the highest percentage of allergic multimorbidity compared to the two other clusters, 100% (A+AD) and 84% A+AD+MFA (Table 1).

Cluster 3, "*Mild peanut* allergic/sensitized *phenotype"* (62 subjects), had the lowest mean disease duration (3.5 years), the lowest proportion of patients with positive OFC (53%) with the highest level of peanut protein inducing a positive OFC (770 mg), a low percentage of allergic multimorbidity (48% A+AD+MFA) and AD only found in a high percentage of cases (95%) (Table 1).

Peanut** allergic/sensitized **phenotypes in subgroup of patients without OFC

Clusters of the subgroup without OFC (n=449) are similar to those of the OFC subgroup (n=247), for most parameters and especially for allergic comorbidities (Table 2). The results were consistent even though the statistical significance of some variables decreased slightly.

Analysis based on gender

Separate cluster analyses were carried out for boys and girls with OFC. These analyses identified the same three clusters as the previous analysis for the boys (Table 3) but only two clusters for the girls (Table 4) i.e. the severe peanut allergic phenotypes called the "*Severe peanut allergy with frequent allergic multimorbidity"and the* "*Severe peanut allergy with little allergic multimorbidity"*.

Discussion

Cluster analysis of the MIRABEL data showed that peanut allergy is a heterogeneous disease. The clustering approach divided the population into two subgroups of severe peanut phenotypes "*Severe peanut allergy with little allergic multimorbidity"* and "*Severe peanut allergy with frequent allergic multimorbidity"* and one non-severe subgroup "*Mild peanut* allergic/sensitized *phenotype".* The severe peanut allergy phenotypes were more frequently encountered in girls.

Strengths and weaknesses

One strength of this study is that it is a multicenter study performed in large population of 696 peanut allergic/sensitized patients recruited by allergists. Moreover, for a large part of this population (almost 250), peanut allergy was diagnosed by OFC, although the reasons for undergoing an OFC or not are not known in this real-life survey. Another strength is that the statistical analyses to identify different phenotypes were conducted by an unsupervised approach with a large range of variables and in a large cohort of patients with severe allergy. The factor analysis was conducted in several steps. A first analysis was performed including all available variables; a second analysis was then conducted excluding variables that were too highly correlated, variables that did not play a large role in explaining the variance, and in combining some variables frequently encountered in patients with multiple food allergies/sensitization. The phenotypes described here remain stable in all the analyses. Moreover, this concordance of three phenotypes (established in patients with and without OFC) highlights the one message of our article, i.e. the importance of multiple comorbidities (especially A+AD or A+AD+MFA) to define a particular phenotype of severe peanut-allergy. One limitation of the study is the different ways in which the OFC was carried out. However, this actually reflects physicians' daily practices and the OFCs selected for analysis were supported by objective symptoms (for positive OFC) and a high dosage of peanut ingested

during OFC (> 7 g of peanut) for the negative test. Similarly, SPTs were not standardized. Another limitation of our study is the heterogeneity of the population, in which patients were probably at different disease stage (for instance, initial diagnosis vs. resolution of peanut allergy). This explains cluster 3 which has the lowest mean disease duration (3.5 years) with the highest proportion of sensitized children. This result is in accordance with the natural history of the disease in which sensitization (more than allergy) is associated with a smaller diameter of the SPT and lower levels of rAra h 2[8]. The clustering algorithms are different when working on the group with OFC and the group without. We consequently analyzed the group with OFC as follows: first using the variables related to the OFC (as presented), and then without the variables related to OFC. Three similar phenotypes were obtained with both methods (data not shown). Therefore, we can conclude that we do not need to have information about OFC to correctly classify a patient into the right cluster. Finally, by our analysis, it was not possible to distinguish at individual level, sensitized or allergic patient, but parameters associated to severe allergic phenotypes (in our cluster analysis) will be taking into account to adapt the schedule of provocation tests.

"Severe peanut allergy with frequent allergic multimorbidity"

This result underlines that allergic multimorbidity (asthma with AD and/or MFA) is associated with a higher reported severity of peanut-induced allergic reactions. Colver et al. showed that asthma was a strongly significant risk factor for severe allergic reactions to food, specifically with peanut[22]. Bock et al. reported similar findings among 32 fatal cases; all of those for whom medical records were available had a history of asthma[23]. Summers et al.[24], in a study of 1,094 patients with tree nut and peanut allergies demonstrated that, as well as severe asthma being associated with life-threatening bronchospasm, severe pharyngeal edema was more common in patients with severe AR. They also found that having severe AD was

associated with a 3-fold increased risk of becoming unconscious during an acute allergic reaction, thus further highlighting the link between the severity of acute allergic reactions and the severity of co-existing atopic disease. We recently described[25], a *"Multiple Allergies and Severe Asthma phenotype"* in which 100% of the children had AD and multiple sensitizations. This is very close to the "*Severe peanut allergy with frequent allergic multimorbidity"* phenotype we present here. This phenotype could correspond to the previously described phenotype of AD associated with filaggrin loss-of-function mutations associated to a greater risk of severe asthma[26].

"*Severe peanut allergy with little allergic multimorbidity" or the high proportion of patients with severe reaction during OFC had a high level of rAra h 2*

This severe phenotype underlines the axis of recombinant rAra h 2 in predicting clinical severity of peanut allergy. rAra h 2 is a heat-stable seed-storage protein and is considered to be the major peanut allergen contributing to peanut sensitization. Peeters et al. looked at whether sensitization to rAra h 1, 2, 3, or 6 can predict the severity of allergic reactions to peanut in a group of 30 patients. They found that patients with severe reactions had a greater SPT response to rAra h 2 and rAra h 6 at low concentrations and to rAra h 1 and rAra h 3 at higher concentrations. They also found that patients with more severe symptoms recognized a greater number of allergens. Sensitization to rAra h 2 plus sensitization to rAra h 1 and/or rAra h 3 was associated with greater severity of reactions[27]. Peptide microarray immunoassays in a group of 77 patients similarly showed that those with wide epitope diversity were associated with a history of more severe allergic reactions[28].

"*Mild peanut* allergic/sensitized *phenotype*" or mild severity of peanut allergy was explained by a high proportion of sensitized patients compared to the other clusters

The subjects in this phenotype were younger at diagnosis, more likely to be sensitized (41.9%), had the lowest positive allergic reaction during OFC, the smallest SPT wheal size, the lowest mean levels of rAra h 2 and a higher percentage of AD (95% of cases). This phenotype could correspond to the current hypothesis that allergic sensitization to food occurs through low-dose cutaneous sensitization[29]. Many studies suggest [30,31,32] that late introduction of potential food allergens and cutaneous exposure[33] might be associated with allergy while early oral exposure might contribute to tolerance. It is thus possible that the young children in our mild peanut phenotype could be in the process of developing real peanut allergy in the case of delayed oral exposure.

More females have the severe phenotypes of peanut allergy: a possible gender effect

The food allergy register has already shown an age-dependent gender distribution, with a M/F sex ratio of 0.67 from early adulthood, in contrast to children where the ratio is 1.50[34]. Similar differences in gender have emerged from several questionnaire-based studies in other countries[35,36]. This observed age-related gender difference is similar to that reported for asthma, hay fever and atopic disease, suggesting that puberty and the influence of sex hormones may have an important impact on the prevalence of atopic diseases in general[37]. In the same vein, a survey reporting on severe allergic reactions defined by the necessity of medical care, showed a higher incidence of food allergy in females. Finally, an Australian study has also reported that females outnumbered males in both acute allergic reactions and anaphylaxis[38].

Conclusions

Our results underline that, beside the classic markers associated with lower threshold doses of OFC (such as SPT or rAra h2), allergic multimorbidity and female gender should also be taken into account to better adapt the progressive dosage of provocation tests.

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Conflicts of interest

A Deschildre reports personal consultancy and lecture fees from GSK, MSD, Aerocrine, MEDA, ALK, Novartis, Stallergènes, Chiesi, outside the submitted work.

J Just reports reports personal consultancy and lecture fees from Novartis, ALK, Stallergènes, Chiesi, phadia, Novartis, GSK, MSD, outside the submitted work.

E Beaudoin reports personal fees from ALK abello SA, MSD, Novartis, outside the submitted work.

The rest of the authors declared that they have no relevant conflicts of interest.

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