Immunobiology 222 (2017) 726–729

Contents lists available at ScienceDirect

Immunobiology

journal homepage: www.elsevier.com/locate/imbio

Short communication

Can pan-allergens affect the sensitization pattern?

Giorgio Ciprandi[a,*], Paola Comite[b], Marco Bruzzone[c], Vincenzo Fontana[c]

[a] Internal Medicine Department, IRCCS-AOU San Martino—IST, Genoa, Italy
[b] Laboratory Medicine, IRCCS-AOU San Martino—IST, Genoa, Italy
[c] Clinical Epidemiology Unit, IRCCS-AOU San Martino—IST, Genoa, Italy

ARTICLE INFO

Article history:
Received 1 January 2017
Received in revised form 20 January 2017
Accepted 22 January 2017
Available online 28 January 2017

Keywords:
Allergen-specific IgE
Pan-allergen
Sensitization
Genoa
Serum

ABSTRACT

The present study tested the hypothesis that a pan-allergen sensitization may affect the sensitization pattern. For this reason, 22 sensitization pattern allergens (SPA), common in Genoa (Italy), were selected for analyses. Successively, five of them, such as Pru p 3 as representative for LTP family, Bet v 1 and Pru p 1 for PR-10, and Bet v 2 and Pru p 4 for Profilin, were used as target allergens (TA). This retrospective study included 1059 subjects, (396 males and 663 females, mean age 42.8 years). The current study showed that sensitization to a pan-allergen entails higher odds to have other sensitizations. In addition, the co-sensitization pattern depends on the basis of the sensitizing pan-allergen family. LTP-sensitization is strongly associated with peanut sensitization, PR10 and profiling sensitization with hazelnut positivity.

This study shows that a pan-allergen sensitization is frequently associated with co-sensitizations and the sensitization pattern depends on the sensitizing pan-allergen.

1. Introduction

Allergic disorders have an impressive impact on healthcare because of high prevalence (WAO, 2017). Sensitization, the ongoing production of allergen-specific IgE, represents the hallmark of the immune response in allergic patients. Documented sensitization is required for diagnosing allergy. Moreover, the natural history of allergy is frequently characterized by an increasing number of sensitizations (the so-called poly-sensitization phenomenon) (Fasce et al., 2007; Melioli et al., 2012). Poly-sensitization is an immunological event that is relevant from an epidemiological and clinical point of view as it ranges from 20% to 90% (Arbes et al., 2005; Baatenburg de Jong et al., 2011; Silvestri et al., 1999). Sensitization can be demonstrated *in vivo* (by skin prick test) or *in vitro* (by serum IgE measurement). The allergen extract mixtures are usually heterogeneous because they may include not only the major allergens, but also cross-reactive allergens, non-allergenic antigens and interfering substances (Brunetto et al., 2010). So, molecular-based allergy diagnostic tests have been recently introduced in the clinical practice, allowing to define and characterize exactly the sensitization profile (Mari et al., 2010). Allergen molecules are directly involved in the specific immune response to allergens. The use of molecular allergens has changed the allergy workup, being highly useful in allergen-specific immunotherapy prescription (Sastre, 2010). In fact, the positivity to major allergens may exclude false reactivity to pan-allergens. Pan-allergen is an allergen molecule that is shared by different allergen sources. In particular, there are some main pan-allergen families: PR-10, profilin, and LTP.

This study was aimed at testing the hypothesis that a pan-allergen sensitization may affect the sensitization pattern. For this reason, 22 sensitization pattern allergens (SPA), common in our geographic area, were selected for analyses. Successively, five of them, such as Pru p 3 as representative for LTP family, Bet v 1 and Pru p 1 for PR-10 family, and Bet v 2 and Pru p 4 for Profilin family, were used as target allergens (TA).

2. Material and methods

2.1. Patients and allergens

This retrospective study included 1059 subjects, (396 males and 663 females, mean age 42.8 years).

The patients went for serologic assessment, as suffered from respiratory and/or food allergy.

The allergens panel included: *Artemisia absinthium* (W5), *Parietaria officinalis* (W19), *Cupressus sempervirens* (T23), olive tree (T9), cat (E1), dog (E5), *Alternaria alternata* (M6), *Dermatophagoides pteronyssinus* (D1), Bet v 1 (T215), Bet v 2 (T216), *Phleum pratense* (G6), milk (F2), fish (F3), wheat (F4), peanut (F17), soybean (F14), hazelnut (F17), shrimp (F24), egg white (F1), Pru p 1 (F419), Pru p

* Corresponding author at: Largo R. Benzi 10, 16132 Genoa, Italy.
E-mail address: gio.cip@libero.it (G. Ciprandi).

http://dx.doi.org/10.1016/j.imbio.2017.01.006
0171-2985/

3 (F420), and Pru p 4 (F421). The study was performed along the 2016.

All patients gave their written informed consent and the Review Board approved the procedure.

2.2. Serum IgE assay

Serum specific IgE was measured by the IFMA procedure (ImmunoCAP Thermo Fisher Scientific, Uppsala, Sweden) according to manufacturer's instructions (Leimgruber et al., 1991). Concentrations were expressed in kUA/L and 0.35 kUA/L has been considered as cut-off for defining positivity, such as sensitization (Seagroatt and Anderson, 1981).

2.3. Statistical analysis

Observed distributions of all allergens were explored and described using arithmetic mean (AM) and standard deviation (ASD), geometric mean (GM), median (P50), interquartile range (IQR) and range of variation (Min-Max). Histograms, QQ-plots and scatterplots were also used to display univariate and bivariate distributions.

Combinations of two allergens, namely F419/T215 (PR-10) and F421/T216 (Profilins), were taken into consideration. In both cases, the "believe the positive" rule was applied: a patient was considered as positive if at least one allergen resulted positive.

Degree of association between binary SPAs and binary TAs was evaluated through logistic regression modelling, using odds ratio (OR), along with corresponding 95% confidence limits (95% CL) as an index of correlation between the proportion of positivity among SPAs and the same proportion among TAs. Log-normal regression modelling was instead applied to estimate the degree of association between log-transformed measurements of SPAs and positive (>0.35 kUA/L) levels of TAs. In this context, the index of association was represented by median ratio (MR) and corresponding 95% CL. MR can be seen as the excess (or deficit) in SPAs per ten-unit increase in each TA. Likelihood ratio test (logistic regression) and Student *t*-test (log-normal regression) were performed to assess the statistical significance of SPA-TA relationships. All regression results were adjusted for potential imbalances in gender and age.

P-value <0.05 was considered as statistically significant. All data were analyzed using the Stata statistical package, Release 13.1 Statistical Software. (StataCorp, College Station, TX. USA).

3. Results

Table 1 shows number and percentage of SPA-positive patients, among those resulted positives to TAs. F420 (LTP) positive tests were 111 among which percentages of SPA-positivity varied from 3.6% to 56.8%, with 4 out of 21 SPAs (D1, F17, G6, W19) >50%. Positivity to F419/T215 (PR-10) concerned 91 patients among whom percentage of positives to SPAs ranged from 4.4% to 85.7%. In this case 7 out of 20 were >50% (D1, E1, E5, F17, G6, T9, W19). Finally, although only 9 patients resulted positive to F421/T216 (Profilin), the range of positivity to SPAs was 33.3%–88.9% and 14 out of 20 tests (D1, E1, E5, F4, F13, F14, F17, F24, F419, GG6, T9, T215, W5, W19) exceeded 50%.

Results of logistic and log-normal regression analyses are displayed in Fig. 1. Logistic regression modelling was applied to binary F420, F419/T215, and F421/T216 (Fig. 1, panel 1, 3 and 6, respectively). In all cases, SPAs were positively correlated to selected TAs: the proportion of positivity among SPAs was always higher than that among TAs. High variabilities around OR estimates pointed out in some circumstances (e.g., F421 in Panel 1; F17 and F421 in Panel 3; F3, F4 and F17 in Panel 6) were essentially due to strong imbalances in the number of patients belonging the two allergen categories.

Choosing OR = 5 as a threshold of a noteworthy SPA-TA relationship, 8 (F3, W5, F4, F421, M6, F17, F14, F13) out of 21 SPAs showed a very high association with dichotomous F420 (Fig. 1, Panel 1), the highest of which is given by F13 (OR = 23.0, 95% CL = 12.5–42.2). As far as binary F419/T215 is concerned (Fig. 1, panel 3), 13 remarkable associations (F13, W5, T9, T23, F3, E5, GG6, M6, T216, E1, F421, W19, F17) among 20 SPAs were pointed out. In this context, the strongest relationship was estimated for F17 (OR = 84.5, 95% CL = 39.1–182.1). Finally, when binary F421/T216 is considered, all ORs exceeded 5, and, also in this case, F17 appeared to be the allergen more highly correlated (OR = 31.4, 95% CL = 3.69–267).

Fig. 1 also displays the log-normal regression results obtained when a gaussian (linear) modelling is applied to log-transformed SPA levels. Overall, all SPAs resulted to be positively correlated to the selected TAs. In particular, using MR = 1.5 as a reference threshold, which means a variation of at least 50% in any SPA per ten-unit increase in the corresponding TA, 7 (F421, F3, W5, F14, F17, F13, F4) out of 21 SPAs exceeded the threshold when compared to F420 (Fig. 1, Panel 2). In particular, F4 showed the maximum median percent variation which was about 77%. Similar results were obtained using F419 as a TA. In this case, 5 (F3, F421, F13, E5, F17) out of 21 SPAs went beyond the reference MR, with F17 showing the highest estimate (MR = 1.61, 95% CL = 1.32–1.95). Finally, when T215 is considered as a TA, only one out of 20 SPAs, namely F17, reported a noteworthy result (MR = 1.58, 95% CL = 1.40–1.78). A very small sample size (7) prevented from performing any further regression analyses on positive measurements of both F421 and T216.

4. Discussion

IgE to pan-allergen assessment is fruitful in the allergy work-up. In this context, a clinical question is: can pan-allergens affect the sensitization pattern? The current study showed that sensitization to a pan-allergen entails higher odds to have other sensitizations. In addition, the co-sensitization pattern depends on the basis of the sensitizing pan-allergen family. LTP-sensitization is strongly associated with peanut sensitization, PR10tization to a pan-allergen entails higher odds to have other sensitizations. In addition, the co-sensitization pattern depends on the basis of the sensitizing pan-allergen family. LTP-sensitization is strongly associated with peanut sensitization, PR10 and profiling sensitization with hazelnut positivity. These findings are consisting with well-known data. Sensitization to Ara h 9 (LTP) is very common in the Mediterranean area (Asero et al., 2002; Laurer et al., 2009; Krause et al., 2009). Sensitization to Cor a 1 (PR-10) is very common in north-central Europe (Pastorello et al., 2002) and Genoa (Tosca et al., 2015). In this regard, it is noteworthy that Genoa is an area with Bet v 1 preeminence despite is birch-free (Tosca et al., 2015). The possible explanation for this paradox may be the abundant presence of *Ostrya carpinifolia*, strong sensitizer toward a Bet v 1-sensitization (Ciprandi et al., 2016). So, Genoa pollen environment, characterized by abundant presence of *Betulaceae* and Parietaria (Par j 2 is a LTP), is a melting-pot able to influence pollen and food sensitizations.

However, the current study had some limitations: it was retrospectively conducted on a selected patient population sample, subjects referring for serologic assessment, there was no follow-up, and there are no clinical data. In addition, other limitations of the current study were the lack of sample stratification considering the season of blood sample throughout the year and the age of the subjects. Therefore, there is need to conduct cohort studies and long-term follow up trials to confirm these preliminary findings. Anyway, the strength of the present study is represented by the large size of the sample: higher than in the other similar studies.