Risk Factors in Severe Anaphylaxis: Which Matters The Most, Food or Cofactors?

Running title: Risk Factors in Anaphylactic Shock

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Abstract

**Background:** The prevalence of anaphylactic shock, the most severe manifestation of anaphylaxis, remains unknown. Risk factors and biomarkers have not been fully identified.

**Objective:** To identify risk factors in anaphylactic shock patients

**Methods:** Using lipid transfer protein (LTP) allergy as a model, the characteristics of patients who developed anaphylaxis and anaphylactic shock were compared. Demographics, pollen sensitization, foods ingested up to 2 hours before the reaction onset, and the presence of a cofactor were recorded. Culprit foods were identified by compatible clinical history and positive allergological work-up (skin prick test and/or sIgE).

**Results:** 150 reactions were evaluated, suffered by 55 patients with An (134 reactions) and 12 with AnS (16 reactions). Patients in the anaphylaxis group experienced twice as many reactions (mean [SD] 2.4[2.5] in An vs 1.3[1.5] in AnS, p<0.02). No relationship between any food group and reaction severity was found. The most frequent food involved in both groups of patients was the combination of several plant-derived foods (“plant food mix”), followed by peach and nuts. Indeed, in the “plant food mix” reactions the presence of a cofactor was more often observed than in other food groups. On the other hand, cofactors were not present in peach- and nuts-related reactions. Exercise was the most frequent cofactor in all groups.

**Conclusion:** In our series, the severity of the reactions was not determined by the kind of food or presence of a cofactor. Anaphylactic shock seems an infrequent presentation that may be related with other individual-related factors that need further evaluation.

**Keywords:** Anaphylaxis. Anaphylactic shock. Cofactor. Food allergy.
Resumen:

Introducción: La prevalencia del shock anafiláctico sigue siendo desconocida. Aun no se han identificado completamente factores de riesgo ni biomarcadores.

Objetivo: identificar factores de riesgo de shock anafiláctico.

Método: Utilizando la alergia a proteína de transferencia de lípidos (LTP) como modelo, se han comparado características de pacientes que han presentado una anafilaxia (An) y pacientes que han desarrollado un shock anafiláctico (SAn). Se recopilaron datos demográficos, sensibilización a pólens, alimentos ingeridos hasta 2 horas antes del inicio de la reacción y la presencia o no de cofactores. El alimento implicado se identificó mediante historia clínica compatible y estudio alergológico positivo (prick test y/o IgE).

Resultados: se evaluaron un total de 150 reacciones; 55 pacientes del grupo An sufrieron 134 reacciones, y 12 pacientes del grupo SAn sufrieron 16 reacciones. El grupo An experimentó el doble de reacciones por paciente (media [DS] 2.4 [2.5] en An vs 1.3 [1.5] en SAn, p<0.02). No se observó relación entre el tipo de alimento y la gravedad de la reacción. El alimento implicado con más frecuencia en ambos grupos fue la combinación de varios vegetales (“mix de vegetales”), seguido por el melocotón y frutos secos. No hubo cofactores implicados en las reacciones con melocotón ni con frutos secos. En ambos grupos el ejercicio fue el cofactor involucrado con más frecuencia.

Conclusión: en nuestra serie, el alimento y la presencia de cofactor no determinan la gravedad de una reacción. Los shocks anafilácticos parecen ser una presentación infrecuente y podrían estar relacionados con factores individuales que precisarán una evaluación más extensa.

Introduction

Anaphylaxis is defined as a severe and life-threatening hypersensitivity reaction[1–3]. Since there is no universally accepted definition, the epidemiological data worldwide is difficult to compare. In anaphylaxis, the most commonly affected organs are the skin, followed by the gastrointestinal and respiratory tract and the cardiovascular system. As observed in the European Anaphylaxis Registry (NORA)[4], respiratory or cardiovascular collapse during anaphylaxis may be fatal due to a distributive shock situation, in which hypoperfusion of vital organs and tissues may cause dysfunction and cell death. Despite its importance, no worldwide epidemiological data are available on anaphylactic shock and only local registries exist[5–7]. The presence of comorbidities such as atopic eczema/dermatitis and asthma[8] or certain triggers such as drugs have been related with more severe anaphylaxis[9,10]. Indeed, there is abundant evidence that the presence of cofactors, such as exercise, alcohol, non-steroidal anti-inflammatory drugs, can increase the severity of the reactions and/or lower the reaction threshold to the allergens[11–16]. However, risk factors specifically linked to anaphylactic shock are still unknown.

Plant foods are one of the most frequent causes of food allergy (FA) worldwide[17–20]. Thaumatin, 2s-albumin and LTP have been associated with severe systemic reactions[21], although not particularly with anaphylactic shock. LTP is one of the most common allergens involved in plant food allergy in the Mediterranean area, but it is becoming more evident that this problem is not as geographically localized as once reported[22]. Several studies from Northern Europe and Asia[23–25] have also shown that LTP allergy is a major concern. The severity of LTP allergy may vary widely[26] and risk factors for severe reactions are not fully identified. Cofactors, as described for other allergens[27,28], may be related with severe reactions in those patients[13]. However, no particular LTP-containing food has been linked to severity[26,29,30]. In any case, LTP allergy is a medical challenge due to the potential severity of the reactions and the number of potential foodstuffs triggering the reactions, including vegetables, nuts, fruits, cereals, and legumes.

In this study we aimed to evaluate a group of patients with LTP allergy who had experienced anaphylaxis, to compare differences between those with anaphylaxis but no shock, to those who experienced anaphylaxis and shock.
Patients and Methods

Patient selection

We consecutively selected adult patients (> 18 years) seen in the Allergy Section of the Hospital Clinic of Barcelona who had a clinical diagnosis of anaphylaxis due to LTP allergy. Patients were classified into two groups according to clinical presentation. The anaphylaxis (An) group included patients who suffered anaphylactic reactions without shock manifestations (grade 3,4), and the anaphylactic shock (AnS) group (grade 5) comprised patients who presented only anaphylactic events with clinical signs of shock as respiratory or cardiovascular collapse according to the to the Anaphylaxis Committee of the World Allergy Organization (WAO) definition[31,32]

Demographic data, pollen sensitization, all foods ingested up to 2 hours before reaction onset and the presence of a cofactor up to 4 hours before reaction onset, including NSAIDs, exercise, alcohol, menstrual cycle, and sleep deprivation were recorded.

Foods were grouped as follows: nuts, prunoideae family, legumes, cereals, vegetables, other fruits and “plant food mix”. The latter was used when more than one LTP-containing food was involved in the reaction (ingested at the same time, in the same meal) and the individual culprit could not be identified by clinical history and/or algological work-up (“Plant food mix” breakdown is in supplementary table 1).

Skin prick testing (SPT) to a panel of aeroallergens and food allergens with commercial extracts and used in the standard practice of our Allergy Section were performed in all patients following standard procedures. It included cypress, olive tree, plane tree, mugwort, wall pellitory, grass pollen, profilin, cow milk, egg, walnut, kiwi, peach, corn, wheat, chickpea, mustard, apple, hake, anisakis simplex, shrimp, melon, green beans, peanut, hazelnut, lettuce, beef, and gliadin [33]. Prick-by-prick with the suspected culprit was performed when a commercial prick test was negative or not available. Total and specific IgE (sIgE) were measured in serum using ImmunoCAP (Phadia, Thermo Fisher Scientific) and values≥ 0.1 kU/L were considered positive. sIgE for the suspected allergenic source and its LTP (when available) were measured. Microarray immunoassay using ImmunoCap ISAC (Phadia, Thermo Fisher Scientific) was also used rule out sensitization to other panallergens and to confirm LTP sensitization; values≥ 0.30 kUA/L were considered positive. “LTP syndrome” was considered when LTPs from plant-food families other than peach or Rosaceae were recognized[26,34,35]
Oral challenge test with suspect foods was dismissed due to the severity of the reactions. The diagnosis is based in a suitable clinical history and confirmed sensitization to the culprit food by skin prick test and/or slgE. In cases in which an NSAID was involved as a suspected cofactor, an oral challenge test was performed in fasting conditions to rule out NSAID hypersensitivity.

Statistical analysis

Statistical analysis was performed using IBM SPSS statistical software. Quantitative variables with normal distribution were described as means with standard deviation (SD), and variables without normal distribution were described as medians with interquartile ranges (IQR). Categorical variables with continuous variables were compared using the parametric Student t-test and ANOVA with the Tukey and Tamhane post hoc test. A p value < 0.05 was considered statistically significant.

Results

Population characteristics

67 patients with LTP-related anaphylaxis were included and divided into two groups according to their clinical manifestations; the anaphylaxis (An) group included 55 patients (82%) and the anaphylactic shock (AnS) group included 12 (18%).

Demographic data, total IgE levels, tryptase, peach and Pru p 3 slgE as a marker of LTP allergy, and nuts LTP slgE(Ara h 9, Cora8, Jug r 3) are shown in Table 1. There were no statistically significant differences in the study variables among groups. LTP slgE levels in AnS patients were lower, although the differences were not significant. In Supplementary Table 1, we specified all food sensitization found by positive SPT (commercial and/or natural extracts) and/or slgE, and the food registered in “Plant-food mix” group reactions. 96% and 91% of the patients in the An group and AnS group respectively, were sensitized to at least one LTP other than Pru p 3 and fulfilled the LTP syndrome definition; median [IQR] number of sensitizations was 2 [3] with no statistically significant differences were observed between groups (Table 2). Profilin sensitization was observed only in 10 patients, 8 in the An group. No other panallergen sensitization was identified.
Food and cofactors involved in anaphylaxis

A total of 150 reactions were observed in 67 patients, 134 (89%) were anaphylaxis and 16 (11%) anaphylactic shocks, distributed as shown in Table 3. Patients in the An group had significantly more reactions per patient than the AnS group (mean [SD] 2.4[2.5] vs 1.3 [1.5], respectively (p = 0.02)).

In both severity groups, the most frequent food involved in the reactions was “plant food mix”, followed by Prunoideae fruits and nuts. Peach and walnut were the most frequent single foods identified as a culprit in the reactions in both groups.

Interestingly, legumes and fruits other than peach were never involved in an anaphylactic shock. Peach was never observed in cofactor-dependent reactions in any of the groups. Nuts were only involved in anaphylactic shock either when associated with cofactor or when several nuts were taken (Table 3).

Cofactors were involved in 43% (58/134) and 38% (6/16) of the reactions in the An and AnS group respectively, with no statistically significant differences between them. The “plant food mix” was the most frequently food group involved in cofactor-dependent reactions, and was significantly more common in the An group [88% (51/58)] than in the AnS group [50% (3/6)] (p = 0.04). Exercise was the most frequent cofactor in all groups; An 33/58[57%] and AnS 3/6 [50%] AnS, with no statistically significant differences between them. Remarkably, more than one cofactor was involved in 9 reactions (8 An and 1 AnS), with no differences among groups (Table 4).

In both groups no differences were observed when sub-analyzing those patients sensitized to both LTP and profilin and comparing them to the group with only LTP sensitization, regarding kind of food and the presence of a cofactor.

Pollen sensitization

We found sensitization to at least one of the LTP-containing pollens tested in our routine panel (olive tree, plane tree, mugwort, and wall pellitory) in 57/66 (86%) patients; most patients (80% [51/64]) suffered pollinosis. Although no significant differences in pollen sensitization or pollinosis were observed between An and AnS groups, olive and plane tree sensitization was higher in the AnS group and mugwort in the An group. Plane tree sensitization was the most frequent in the overall groups, with no differences between them (Table 5).
Discussion

The prevalence of anaphylactic shock, the most severe manifestation of anaphylaxis, is still unknown and the risk factors associated with this entity are poorly defined. In this study, we compared the characteristics of two sets of patients who developed anaphylaxis and anaphylactic shock using LTP allergy as a model. According to the sensitization pattern, we observed that more than 90% of our patients were sensitized to different LTPs, in line with the results of other Spanish series[36,37], underlining the burden of LTP syndrome in our country.

In our study, individuals suffering anaphylaxis had almost twice as many reactions per patient than those suffering anaphylactic shock. This may be an expected result because after having experienced an extremely severe reaction such as anaphylactic shock, patients are probably more careful with their diet and/or referred to an allergist faster than individuals with milder anaphylaxis,(grade 3 according to WAO definition [32]) who are frequently overlooked[38]. Another hypothesis is that the occurrence of an anaphylactic shock may be linked to some predisposition related with some yet-to-be-identified factors that are present only in some individuals. Genetic mutations as observed in patients with systemic mastocytosis, or the KARS gene mutation recently described in one patient with extremely severe hymenoptera allergy[39] or defects on some of the compensatory mechanisms[40]such as prostaglandin E2 as recently observed in hymenoptera venom[41]and LTP allergy patients[42]may be some of these predisposing factors in those who developed life-threatening anaphylaxis.

We did not find any obvious relationship between food type and severity, but there were some interesting observations. When all reactions were pooled, most patients (54%) needed several LTP-containing foods in the same meal to develop a reaction. This observation is in line with the everyday habits of our population which culturally follows a Mediterranean diet, where it is usual to mix vegetables, fruits, legumes and cereals, all containing LTP, in the same meal. Thus, in some cases it was not possible to identify whether the trigger was just one of the plant foods, or the cumulative dose of LTPs from the different sources, considering that the patients were sensitized to all of them. Interestingly, “plant food mix” was also the most frequent food group in overall cofactor-dependent reactions (An 88%, AnS 50%), with significant differences irrespective of severity. In a series of cofactor-dependent food allergy patients[13,15]lettuce and wheat were the plant foods most frequently involved in those reactions.

Peach was the single food most often involved in both anaphylaxis and anaphylactic shock in our study. This is unsurprising, given that peach is the most common cause of food allergy in Spain, Italy and Portugal, mainly due to LTP sensitization[43]. Indeed, peach is considered the
primary sensitizer in LTP allergy in southern Europe and for this reason it is considered the prototypic marker of LTP sensitization[44]. Interestingly, all peach-related reactions in our study were cofactor-independent. Similarly, some series of cofactor-dependent LTP-related reactions, have shown almost no peach-related reactions [13,15].

Walnut was the second single food most frequently involved in the anaphylaxis group, with no anaphylactic shocks reported. Tree nut allergy accounts for up to 40% of food-induced anaphylactic fatalities, and in some cases tree nut reactions have been reported to be more severe than reactions to peanut[45]. In a recent study by Ballmer-Weber et al. comparing walnut allergy patients from Spain, Germany and Switzerland, Jug r 1 but not Jug r 3 (walnut LTP) sensitization was significantly associated with systemic reactions. Interestingly, in our series, nuts were only involved in anaphylactic shock when associated with a cofactor or when several nuts were consumed together.

Legumes were only related with cases of anaphylaxis without shock, and no cofactors were involved. Legumes, excluding peanut, are an important cause of allergy in some geographical areas, mainly in children[46], and several allergens have been described, including LTP[47]. Some of these allergens, such as 2S albumins, have been associated with severe reactions[48,49], but almost no data is available on the characteristic of LTP-dependent reactions in legume allergy patients.

Taking all these observations together, we could speculate whether the LTPs from different allergenic sources might have different capacities to induce an allergic reaction, and for this reason, while some allergenic sources usually “need” a cofactor, others, like peach, are able to induce severe reactions by themselves. Another interesting observation, as yet unresolved, is the amount of LTP needed to develop a severe reaction. This may be related with the particular allergenic source, the way is consumed (cooked or raw) and, perhaps, personal predisposition[50]. However, the studies performed by M. Christensen et al [51] an Brockow et al [52] in wheat-dependent exercise-induced anaphylaxis (WDEIA) would suggest that increasing the amount of allergen may suffice to both decreased the threshold level and increase the severity of the reaction in the absence of a cofactor in any patient and regardless the characteristic of the original reaction. For this reason, although other studies are needed, It is maybe important to identify all food sensitization in LTP allergic patients even if they are apparently asymptomatic[53,54]. Although these foods by themselves may not be inducing any reaction, together with enough amount of other LTP-containing allergic sources may be contributing to the development of the final reaction.
In our series, the most frequent cofactors involved in both anaphylactic and anaphylactic shock groups was exercise (57% and 50% respectively), followed by NSAIDs. Using data from the “The European Anaphylaxis Registry”[55]. Worm et al[56] observed that vigorous, but not mild or moderate, exercise was a risk factor for more severe food-dependent reactions (OR 2.06, p < 0.0001). Christensen et al[57] showed that NSAID is the most powerful cofactor in WDEIA patients, decreasing the threshold by 83%, compared to 63% observed in exercise or 36% in alcohol. Interestingly, we observed a non-negligible rate of 14% of patients who needed more than one cofactor. This may be quite an everyday life situation, for instance in women taking an NSAID for menstrual cramps, or people drinking alcohol and dancing after dinner. Although we did not find that several cofactors were related with severity, in WDEIA patients, NSAIDs and exercise together decreased the allergen threshold by 87% showing a partially additive effect[57].

Most patients in our study were women, both in the anaphylactic and anaphylactic shock groups. Previous studies have suggested that oestrogens were associated with more severe reactions in mice [58], and male sex was mainly related with insect venom-related anaphylaxis [59]. Conversely, Worm et al. [56] in a study based in the NORA registry, male sex was associated with a higher risk of severe anaphylaxis irrespective of the elicitor, including food, drugs or hymenoptera venom. Our study is limited not only to foods, but to LTP-related reactions. In previous series of LTP allergic patients, mostly with anaphylaxis, a slightly higher prevalence of females (around 60%) has been observed [22,60,61]. Together with our findings, these observations may suggest that LTP allergy may be more prevalent in females, rather than that severity is gender-related.

In our series, patients were sensitized to all plant foods involved in the reactions due to LTP recognition. No other panallergens but profilin were identified in a small number of our patients. Although profilin has been related with food anaphylaxis[62,63] we believe that in those double sensitized patients (LTP and profilin) reactions were induced by LTP or both LTP and profilin, but it is unlikely that symptoms were only related to profilin sensitization. Furthermore, we did not find any relation between reaction severity and profilin sensitization as other authors did. Bogas et al. [64] in a series of more than 250 Spanish LTP allergic patients from two different geographical areas that include Barcelona, found that double sensitized (profilin and LTP) patients had less peach anaphylaxis compare to those sensitized to only LTP. However, these authors did not compared the impact of profilin in anaphylaxis severity. In our sample, 13 of 55 patients from the An group had a reaction with peach, but only 2 of them [2/13 (15%)] were sensitized to profilin. On the other hand, in the AnS group none of the 3

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patients who reacted with peach (3/12), had a double sensitization. Therefore, we found a low proportion of cases with double sensitization as in Bogas et al. study, but we would need a larger sample in order to draw conclusions in the “protective role” of profilin in different severities of anaphylaxis.

Pollinosis, unlike described in other series (65), had no influence in either increasing or decreasing the severity of the reactions in our patients. Plane tree sensitization was the most common, as expected for two main reasons. Plane tree pollen is the most frequent sensitization observed in respiratory allergic patients in Barcelona (37%) [66]. However, its prevalence in LTP-allergic patients is even higher as previously shown by Enrique et al [67] in 2002, when plane tree sensitization was observed in 8% of the respiratory allergic patients and in 55% of those with LTP food allergy. Cross-reactivity due to LTP in plane tree pollen and plant foods may account for this observation. Mugwort was the second most frequent pollen sensitization, but plane tree, with no clinical relevance in our area and related to LTP cross-reactivity as previously described[68].

One of the limitations of this study is the recall bias; the particularities of the reaction, including food and cofactors, were collected some time after the acute reaction and therefore, some relevant information may be missing. However, this is a real-life situation, in which avoidance recommendations and advice are based on the information offered by the patients. The small number of anaphylactic shocks, and some other important factors that may be related with severity, such as delay in seeking medical attention and epinephrine administration, that were not evaluated in this study may also limit the results.

In conclusion, we did not find any risk factors for anaphylactic shock in the study variables, and neither individual foods nor cofactors seem to be associated with severity, although further studies with a larger sample are needed to confirm these observations. However, our results suggest that every LTP source may have different capability to induce severe reactions. For this reason the risk of having an LTP-dependent anaphylaxis may be depending on a particular combination of several factors that may be patient-dependent, including the allergenic source, the amount of allergen (cumulative dose), the presence of cofactors as well as a personal predisposition.
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### Tables

**Table 1.** Demographic data of patients with anaphylaxis and anaphylactic shock.

<table>
<thead>
<tr>
<th></th>
<th>An group</th>
<th>AnS group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=55</td>
<td>n=12</td>
<td></td>
</tr>
<tr>
<td>Age mean [SD]</td>
<td>42.35 [12.41]</td>
<td>40.67 [11.68]</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (female); n/total</td>
<td>36 (65.45%)</td>
<td>9 (75%)</td>
<td>NS</td>
</tr>
<tr>
<td>Total IgE</td>
<td>144 [60.8-287.5]</td>
<td>108 [28.7-177]</td>
<td>NS</td>
</tr>
<tr>
<td>Peach sIgE</td>
<td>4.4 [1.5-11.7]</td>
<td>4.6 [0.8-10.8]</td>
<td>NS</td>
</tr>
<tr>
<td>Pru p3 sIgE</td>
<td>5.8 [2-13.3]</td>
<td>3.7 [0.4-9.5]</td>
<td>NS</td>
</tr>
<tr>
<td>Ara h 9 sIgE</td>
<td>1.8 [0.5-4.8]</td>
<td>1.3 [0.3-5.4]</td>
<td>NS</td>
</tr>
<tr>
<td>Cor a 8 sIgE</td>
<td>0.9 [0.3-9.2]</td>
<td>0.8 [0.2-2.5]</td>
<td>NS</td>
</tr>
<tr>
<td>Jug r 3 sIgE</td>
<td>2.3 [0.5-1.7]</td>
<td>1 [0.4-3.6]</td>
<td>NS</td>
</tr>
<tr>
<td>Basal tryptase</td>
<td>4.1 [2.9-5.7]</td>
<td>3.8 [3-4.4]</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are expressed as median [IQR] unless otherwise stated. sIgE expressed as kU/L, An: anaphylaxis, AnS: anaphylactic shock, IQR: interquartile range, NS: not significant. *p-value >0.05*, SD: standard deviation.
**Table 2.** Sensitization profile of LTP syndrome patients.

<table>
<thead>
<tr>
<th>Number of LTP sensitizations</th>
<th>Anaphylaxis $n=50$</th>
<th>Anaphylactic shock $n=11$</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n$ (%)</td>
<td>$n$ (%)</td>
<td></td>
</tr>
<tr>
<td>Pru p 3 monosensitized</td>
<td>2 (4)</td>
<td>1 (9)</td>
<td>NS</td>
</tr>
<tr>
<td>Pru p 3 + 1 LTP</td>
<td>4 (8)</td>
<td>1 (9)</td>
<td>NS</td>
</tr>
<tr>
<td>Pru p 3 + 2 LTPs</td>
<td>8 (16)</td>
<td>3 (27)</td>
<td>NS</td>
</tr>
<tr>
<td>Pru p 3 + 3 LTPs</td>
<td>36 (72)</td>
<td>6 (55)</td>
<td>NS</td>
</tr>
</tbody>
</table>

LTP: lipid transfer protein, NS: not significant $p$-value $>0.05$
Table 3. Food and cofactors involved in the reactions.

<table>
<thead>
<tr>
<th>FOOD GROUP</th>
<th>ANAPHYLAXIS</th>
<th>ANAPHYLACTIC SHOCK</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 134</td>
<td>n = 16</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nº of reactions (%)</td>
<td>Food-disaggregated nº of reactions</td>
<td>Nº of reactions (%)</td>
</tr>
<tr>
<td>Prunoideae</td>
<td>16 (12)</td>
<td>Peach (14) Cherry (2*)</td>
<td>3 (19)</td>
</tr>
<tr>
<td></td>
<td>2* (13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Plant food mix”</td>
<td>77 (57)</td>
<td>Peanut (3)</td>
<td>8 (50)</td>
</tr>
<tr>
<td></td>
<td>51* (66)</td>
<td></td>
<td>3* (38)</td>
</tr>
<tr>
<td>Nuts</td>
<td>15 (10)</td>
<td>Peanut (3) Walnut (5) Hazelnut (2) Several nuts (5)</td>
<td>2 (13)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2* (100)</td>
</tr>
<tr>
<td>Other vegetables</td>
<td>9 (7)</td>
<td>Lettuce (3;1*) Tomato (2;1*) Cabbage (2*) Sunflower seed (2;1*)</td>
<td>2 (13)</td>
</tr>
<tr>
<td></td>
<td>5* (56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cereals</td>
<td>3 (2)</td>
<td>Wheat (2) Corn (1)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Legumes</td>
<td>4 (3)</td>
<td>Chickpea (1) Lentil (1) Green bean (2)</td>
<td>-</td>
</tr>
<tr>
<td>Other fruits</td>
<td>10 (7)</td>
<td>Banana (1) Apple (2) Orange (1) Pomegranate (1) Grape (2) Pear (2) Strawberry (1)</td>
<td>-</td>
</tr>
</tbody>
</table>

Asterisk (*): number of cofactor-dependent reactions.
NS: not significant p value > 0.05
Table 4. Cofactors involved in the reactions.

<table>
<thead>
<tr>
<th></th>
<th>Anaphylaxis</th>
<th>Anaphylaxis Shock</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 58</td>
<td>n = 6</td>
<td></td>
</tr>
<tr>
<td><strong>Nº of reactions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAID</td>
<td>15(26)</td>
<td>2(33)</td>
<td>NS</td>
</tr>
<tr>
<td>Exercise</td>
<td>33(57)</td>
<td>3(50)</td>
<td>NS</td>
</tr>
<tr>
<td>Alcohol</td>
<td>2(3)</td>
<td>0(0)</td>
<td>NS</td>
</tr>
<tr>
<td>Several cofactors</td>
<td>8(15)</td>
<td>1(17)</td>
<td>NS</td>
</tr>
</tbody>
</table>

An: anaphylaxis, AnS: anaphylactic shock, NS: not significant p value >0.05; NSAID: non-steroid anti-inflammatory drugs.
### Table 5. Pollen sensitization profile

<table>
<thead>
<tr>
<th>Pollensensitization</th>
<th>Anaphylaxis ( n = 52 )</th>
<th>Anaphylactic Shock ( n = 12 )</th>
<th>( p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n(%) )</td>
<td>( n(%) )</td>
<td></td>
</tr>
<tr>
<td><strong>Olivetree</strong></td>
<td>16(31)</td>
<td>5(42)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Planetree</strong></td>
<td>33(63)</td>
<td>10(83)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Mugwort</strong></td>
<td>29(56)</td>
<td>4(33)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Wall pellitory</strong></td>
<td>15(29)</td>
<td>3(25)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Profilin</strong></td>
<td>8(15)</td>
<td>2(17)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Pollinosis</strong></td>
<td>42(81)</td>
<td>9(75)</td>
<td>NS</td>
</tr>
</tbody>
</table>

An: anaphylaxis, AnS: anaphylactic shock, NS: not significant \( p \) value >0.05