

Anaphylactic versus Mild Reactions to Hazelnut and Apple in a Birch-Endemic Area: Different Sensitization Profiles?

T.M. Le E. van Hoffen A.F.M. Lebens C.A.F.M. Bruijnzeel-Koomen A.C. Knulst

Department of Dermatology and Allergology, University Medical Center Utrecht, Utrecht, The Netherlands

Key Words

Apple and hazelnut allergy · Birch pollen · Lipid transfer protein

Abstract

Background: Hazelnut and apple are common causes of food allergy in Europe. In northern Europe, symptoms are usually mild and associated with cross-reactivity to the birch pollen allergen, Bet v 1. In the Mediterranean area, symptoms are more frequently severe and associated with sensitization to lipid transfer protein (LTP). This study compared patients with anaphylactic versus mild reactions to hazelnut and apple in The Netherlands, a birch-endemic area, with respect to sensitization to Bet v 1-homologues (i.e. PR10-proteins) and LTP. **Methods:** Twenty-one patients fulfilling the criteria for anaphylaxis and 21 with only mild symptoms (oral allergy) to hazelnut and/or apple were recruited. Specific immunoglobulin E to birch pollen, apple, hazelnut and PR10-proteins (rBet v 1, rPru p 1, rMal d 1 and rCor a 1) and recombinant LTP (rPru p 3 and rCor a 8) was measured by ImmunoCAP. **Results:** Both mild and anaphylactic apple-allergic patients were sensitized to PR10-proteins, whereas only 1/7 of the mild and none of the anaphylactic apple-allergic patients was sensitized to LTP. In contrast, anaphylactic hazelnut-allergic patients displayed no such clear sensitization pattern: some were sensitized to both PR10-proteins and hazelnut LTP (1/9), and others to only LTP (2/9) or to only PR10-proteins (4/9) or to neither PR10-proteins nor LTP (2/9). **Conclusion:** This study shows that in a birch-endemic area, the sensitization profile to PR10-proteins and LTP in anaphylactic patients may differ between different plant foods. In this patient group, anaphylaxis to hazelnut can be LTP-associated, whereas anaphylaxis to apple is not.

Copyright © 2012 S. Karger AG, Basel

Introduction

Hazelnut and apple are common causes of food allergy in Europe [1, 2]. There seem to be geographic differences in the sensitization route, allergen recognition and clinical severity in patients with plant food allergies [3–6]. In northern and central Europe, where birch pollen is common, hazelnut and apple allergy are often a result of a primary sensitization to birch pollen. This birch pollen-related food allergy is caused by cross-reactive structures between the major birch pollen allergen Bet v 1 and its homologues in hazelnut (Cor a 1) and apple (Mal d 1) [3, 5–7]. The immunoglobulin E (IgE)-binding sites on Bet v

1 homologues are sensitive to heating and digestion [8]. Therefore, symptoms are usually mild and restricted to the oral cavity [9]. Bet v 1 and its homologues are members of the PR-10 family.

In the Mediterranean area, where birch trees are rare, hazelnut and apple allergy are more frequently severe and associated with sensitization to lipid transfer protein (LTP) [3, 4, 6, 7]. The first fully characterized allergenic LTP was Pru p 3, the major allergen of peach [10]. LTPs have also been identified for hazelnut (Cor a 8) and apple (Mal d 3) [3, 6]. Because LTP is a stable allergen, resistant to heat and digestion, it has been considered to be responsible for more severe allergic reactions [11, 12]. Previous studies in northern and central European countries demonstrated that patients with plant-derived food allergies rarely had IgE to LTP [3, 5, 7]. A limitation of the studies so far is that only a few patients with severe reactions were included from birch-endemic areas [3, 5–7]. This is probably due to the fact that severe reactions to hazelnut and apple occur less frequently than, for example, to peanut. Nevertheless, severe reactions to plant-derived foods do also occur in birch-endemic areas [13, 14].

The aim of this study was to compare patients with anaphylactic versus mild reactions to hazelnut and apple in a birch-endemic area with respect to sensitization to PR10-proteins and LTP.

Methods

Patients

Twenty-one patients with anaphylactic reactions to hazelnut and/or apple were recruited from the tertiary allergy centre of the Department of Dermatology and Allergology of the UMC Utrecht in The Netherlands, from August 2003 to March 2008. All patients fulfilled the criteria for anaphylaxis as proposed by Sampson et al. [15]: patients had symptoms of at least 3 organ systems (of the mucous membranes/skin, gastro-intestinal and respiratory systems) or symptoms of the mucous membranes/skin with hypotension. Food challenges were not performed because of the severity of the symptoms [3, 4]. Twenty-one patients with a suggestive history of hazelnut and/or apple allergy and with only mild local symptoms (i.e. oral allergy symptoms) were randomly recruited as controls. All patients had a positive CAP system or skin prick test (SPT) to the allergen (hazelnut and/or apple) to which they were allergic. The study was approved by the local ethical committee.

Detection of Serum IgE

Measurement of specific IgE (sIgE) to birch pollen, hazelnut, apple, PR10-proteins (rBet v 1, rCor a 1, rMal d 1 and rPru p 1) and recombinant LTP (rCor a 8 and rPru p 3) were performed by ImmunoCAP (Phadia, Uppsala, Sweden). sIgE values of ≥ 0.35 kU_A/l were regarded as positive.

Skin Prick Tests

SPTs were performed using commercially available extracts from birch pollen, apple and hazelnut (ALK-Abelló, Nieuwegein, The Netherlands). The SPT was performed and recorded as described by Dreborg [16].

Statistical Analysis

The χ^2 test was used to test differences between patients with anaphylactic reactions and those with mild reactions. The Mann-Whitney U test was used to test differences in the median of IgE levels between these 2 groups. Statistical analysis was performed using SPSS version 15 (2007, SPSS Inc., Chicago, Ill., USA) for Windows. *p* values of <0.05 were considered significant.

Results

Patient Characteristics

Patient characteristics are summarized in table 1. There were no differences with respect to gender and age between the patients with anaphylactic as opposed to mild symptoms (female 14/21 vs. 11/21 with *p* = 0.35; mean age 31 years $\pm$ SD 12 years vs. 31 years $\pm$ SD 11 years with *p* = 0.91). All 42 patients had at the least a positive sIgE or SPT for hazelnut and/or apple; 37 (88%) were also birch pollen-allergic (i.e. with a history suggesting allergy and a positive CAP and/or SPT). In the anaphylactic group, reactions occurred exclusively to hazelnut in 9 patients, to apple in 6 and to both hazelnut and apple in 6. These subgroups will be referred to further as hazelnut-only, apple-only and hazelnut-apple group. In the mild-reaction group, the numbers of patients in these subgroups were 2, 7 and 13, respectively.

LTP- and Bet v 1-Sensitization in the Overall Patient Group

Taking all patients together, 9/42 (21%) had sIgE to LTP (9 to Pru p 3 and 5 also to Cor a 8). Sensitization to LTP did not differ between the anaphylactic and mild-reaction groups (6/21 vs 3/21, *p* = 0.45) and nor did sIgE to PR10-proteins (16/21 vs. 19/21; *p* = 0.41). The IgE levels of LTP and PR10-proteins did not differ between the 2 groups (r Bet v 1: 7.9 vs. 23.8, r Pru p 1: 3.2 vs. 11.0, Cor a 1: 4.4 vs. 17.9, Mal d 1: 1.7 vs. 8.0, Pru p 3: 0.03 vs. 0.02 and Cor a 8: 0.02 vs. 0.01; all *p* values >0.05). In the following paragraphs, sensitization to LTP and PR10-proteins and the association with mild or anaphylactic reactions will be described separately for the subgroups (hazelnut-only, apple-only or hazelnut-apple).

Table 1. Patient characteristics

ID	Age	Sex	Group	Symptoms	BP	CAP								SPT			
						HN	Apple	Birch	rCor a 1	rMal d 1	rBet v 1	rPru p 1	rCor a 8	rPru p 3	Birch	Apple	HN
Hazelnut-only group																	
1	33	m	A	OAS TT CO NA SA DY	Yes	52.2	0.7	<0.35	<0.35	<0.35	<0.35	<0.35	3.5	7.7	1+	1+	3+
2	26	m	A	TT IT ER DY HY	Yes	<0.35	0.35	1.9	3.7	1.5	5.3	0.7	<0.35	<0.35	3+	1+	1+
3	20	f	A	OAS TT NA VO SA DY LC	No	3.8	nd	4.4	3.4	1.1	4.5	1.2	<0.35	<0.35	nd	nd	nd
4	21	f	A	TT RH ER NA VO SA DY	No	1.4	<0.35	<0.35	<0.35	<0.35	<0.35	<0.35	<0.35	<0.35	0	0	0
5	19	f	A	OAS TT CO IT ER UR NA SA DY	Yes	29.4	nd	nd	0.4	<0.35	<0.35	<0.35	<0.35	<0.35	2+	0	3+
6	29	m	A	OAS TT RH CO IT ER UR NA VO SA DY LC	Yes	8.9	52.4	1.9	<0.35	<0.35	<0.35	<0.35	39.3	65.0	0	1+	2+
7	26	m	A	OAS TT IT ER NA VO SA DI DY HY	Yes	2.4	2.9	3.0	1.4	0.9	2.2	1.0	0.7	1.8	2+	2+	1+
8	18	f	A	AE, TT, UR, NA, VO, SA, DI, DY, LC, HY	No	5.4	<0.35	<0.35	<0.35	<0.35	<0.35	<0.35	<0.35	<0.35	0	0	3+
9	25	m	A	TT IT NA VO DY	Yes	5.6	2.7	4.9	2.9	1.3	3.7	1.8	<0.35	1.1	3+	3+	2+
10	19	m	M	OAS	Yes	5.9	0.5	2.7	1.4	0.5	2.1	0.35	<0.35	<0.35	3+	1+	1+
11	23	m	M	OAS	No	4.4	0.6	0.5	<0.35	<0.35	<0.35	<0.35	<0.35	<0.35	0	0	1+
Apple-only group																	
12	15	m	A	OAS TT ER UR VO DY	Yes	15.8	3.9	28.2	21.2	17.7	27.5	18.0	<0.35	<0.35	nd	nd	nd
13	46	f	A	TT RH CO NA VO DY HY	Yes	7.6	0.6	18.3	8.9	5.4	18.0	6.5	<0.35	<0.35	3+	3+	2+
14	38	f	A	OAS CO NA DY	Yes	4.3	0.5	9.7	4.4	1.7	7.9	3.2	<0.35	<0.35	3+	3+	0
15	18	f	A	OAS TT CO IT ER ER SA DY	Yes	130.1	21.8	244.9	253.7	139.7	275.0	237.1	<0.35	<0.35	1+	4+	1+
16	51	f	A	OAS TT RH NA DY	Yes	32.0	3.3	54.6	33.4	15.0	39.0	8.2	<0.35	<0.35	4+	3+	3+
17	31	f	A	OAS RH CO IT NA SA DI DY	Yes	10.7	2.3	31.4	14.0	12.5	29.5	15.1	<0.35	<0.35	3+	4+	1+
18	21	m	M	OAS	Yes	6.4	3.4	26.4	4.9	3.2	18.9	11.0	<0.35	<0.35	3+	3+	2+
19	21	m	M	OAS	Yes	22.4	2.1	66.7	22.8	16.0	48.6	20.4	<0.35	<0.35	4+	2+	2+
20	46	f	M	OAS	Yes	29.1	4.0	39.3	30.0	19.7	28.4	16.7	<0.35	<0.35	2+	4+	2+
21	17	f	M	OAS	Yes	49.7	8.5	89.5	75.1	49.2	95.4	40.2	<0.35	<0.35	4+	4+	2+
22	27	f	M	OAS	Yes	2.1	0.35	4.2	2.1	0.8	2.8	0.9	0.5	4.2	nd	nd	nd
23	56	f	M	OAS	No	5.9	0.35	15.4	6.0	3.0	12.1	2.4	<0.35	<0.35	3+	3+	3+
24	46	f	M	OAS	Yes	5.8	1.1	8.0	5.1	1.6	5.2	1.5	<0.35	<0.35	4+	1+	nd
Hazelnut-apple group																	
25	33	f	A	OAS TT CO IT ER UR NA VO SA DY	Yes	19.3	3.5	37.7	22.6	8.9	39.8	17.7	<0.35	<0.35	2+	nd	nd
26	36	f	A	OAS TT RH CO SA DI DY	Yes	112.3	6.7	119.9	178.1	46.0	132.7	53.1	<0.35	<0.35	2+	2+	2+
27	39	m	A	OAS TT CO IT ER NA VO SA DI DY	Yes	11.3	3.1	30.0	13.4	7.9	34.4	12.9	<0.35	0.6	nd	nd	nd
28	66	f	A	OAS TT RH RH CO IT ER UR DI DY HY	Yes	2.8	1.4	4.0	<0.35	<0.35	<0.35	<0.35	<0.35	<0.35	0	0	0
29	25	f	A	OAS TT RH ER DI DY SA	Yes	5.9	38.0	> 100	214.8	121.3	23.2	132.5	<0.35	0.5	3+	1+	1+
30	23	f	A	OAS TT RH RH CO IT ER SA DI DY	Yes	65.4	6.2	101.8	84.2	40.4	86.2	24.2	<0.35	<0.35	3+	3+	2+
31	46	m	M	OAS	Yes	107.7	32.8	185.1	120.7	66.3	183.7	147.6	<0.35	<0.35	4+	4+	2+
32	32	f	M	OAS	Yes	18.2	2.8	33.3	17.9	5.4	23.8	10.4	<0.35	<0.35	nd	nd	nd
33	28	f	M	OAS	No	1.2	25.0	<0.35	<0.35	<0.35	<0.35	<0.35	3.0	30.5	0	0	1+
34	17	m	M	OAS	Yes	52.4	2.4	224.6	71.1	10.2	123.2	35.7	<0.35	<0.35	3+	3+	3+
35	24	f	M	OAS	Yes	<0.35	0.4	19.3	11.1	0.7	19.5	2.2	<0.35	<0.35	2+	2+	3+
36	31	m	M	OAS	Yes	34.5	nd	nd	47.4	nd	58.8	33.1	<0.35	<0.35	4+	3+	2+
37	41	f	M	OAS	Yes	0.6	0.4	40.1	33.7	40.1	48.7	10.9	<0.35	<0.35	3+	0	1+
38	39	f	M	OAS	Yes	>100	45.0	>100	121.8	>100	131.7	83.2	<0.35	1.1	2+	3+	1+
39	20	m	M	OAS	Yes	1.4	5.0	68.0	12.5	68.0	20.7	11.4	<0.35	<0.35	2+	3+	2+
40	28	m	M	OAS	Yes	14.2	2.7	20.6	14.3	20.6	18.0	4.7	<0.35	<0.35	3+	3+	4+
41	38	f	M	OAS	Yes	70.0	4.5	126.1	86.8	126.1	135.7	43.4	<0.35	<0.35	3+	3+	3+
42	29	m	M	OAS	Yes	86.4	11.4	127.4	68.8	127.4	84.6	41.2	<0.35	<0.35	3+	4+	2+

A = Anaphylactic; BP = a history suggesting birch pollen allergy; CO = conjunctivitis; DI = diarrhoea; DY = dyspnoea; ER = erythema; HN = hazelnut; HY = hypotension; IT = itch; LC = loss of consciousness; M = mild; NA = nausea; OAS = oral allergy symptoms; RH = rhinitis; SA = stomach ache; TT = tightness of the throat; UR = urticaria; VO = vomiting.

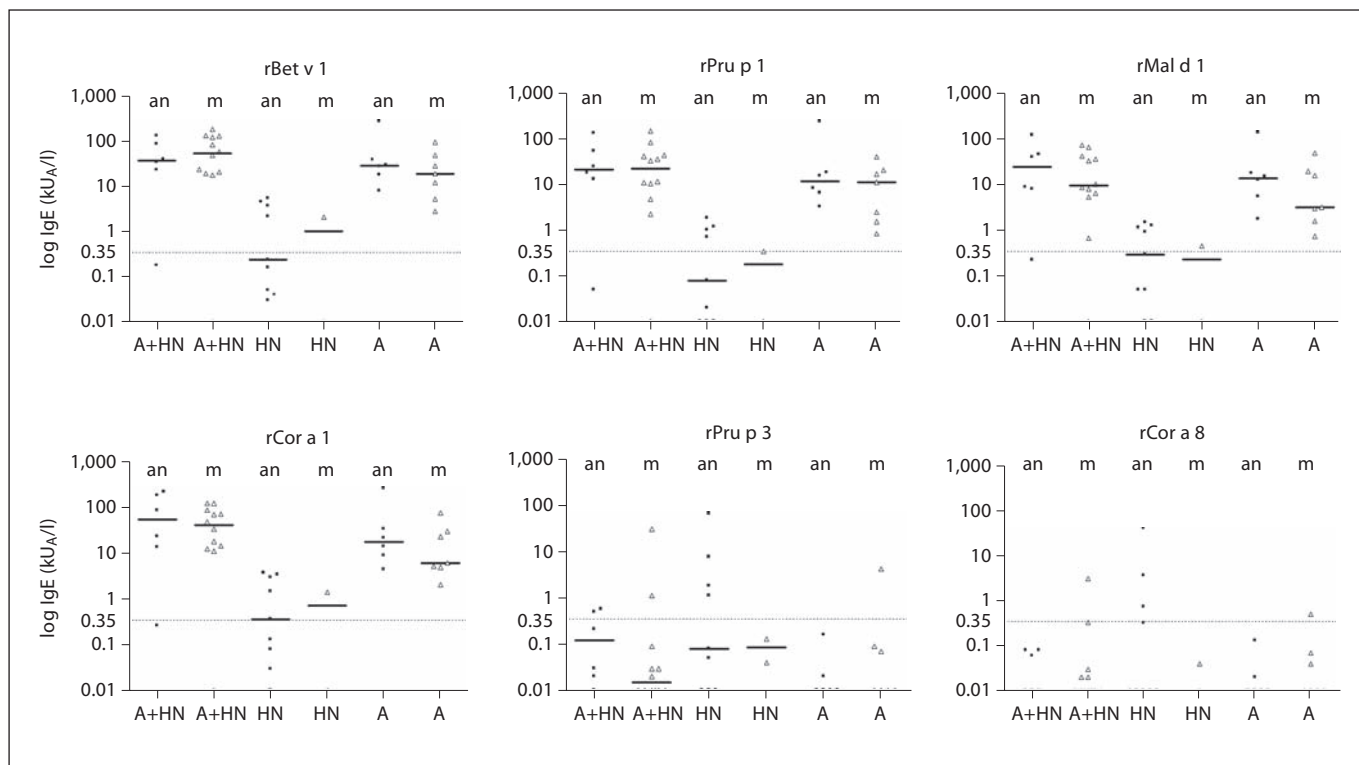


Fig. 1. IgE levels for Bet v 1 and LTP (homologues) in patients with anaphylaxis and mild symptoms. The median value for each data set is marked by a short horizontal line. Dotted lines indicate cut-off value of 0.35 kUA/l. A = Apple-allergic patients; A+HN = patients with apple and hazelnut allergy; an = patients with anaphylaxis; HN = hazelnut-allergic patients; m = patients with only mild symptoms.

Comparison of Mild-Reaction versus Anaphylactic Hazelnut-Only Patients

Noteworthy is that in the hazelnut-only group, patients who had a mild reaction to hazelnut only were scarce; therefore, comparison between the anaphylactic ($n = 9$) and the mild hazelnut-only-allergic patients ($n = 2$) was difficult. Hazelnut LTP, Cor a 8, was recognized by anaphylactic patients but not by patients with mild symptoms (3/9 vs. 0/2, $p = 1.00$). Regarding PR10-proteins, no differences were observed in the sensitization rate (5/9 vs. 1/2, $p = 1.00$) nor in sIgE levels between the anaphylactic and the mild-reaction group (fig. 1). Of the anaphylactic hazelnut-allergic patients, 3/9 did not recognize Cor a 8 or PR10-proteins, indicating that these allergens seem to not be involved in the allergic reaction for some patients.

Comparison of Mild-Reaction versus Anaphylactic Apple-Only Patients

In the apple-only group, no differences were seen in LTP sensitization between anaphylactic and mild-reac-

tion patients (0/6 vs. 1/7, $p = 1.00$). All patients with anaphylactic or mild reactions to apple were sensitized to PR10-proteins and there were no differences in sIgE levels (r Bet v 1, 28.5 vs. 18.9; r Pru p 1, 11.7 vs. 11.0; Cor a 1, 17.6 vs. 6.0; Mal d 1, 13.7 vs. 3.2, all p values >0.05 , fig. 1).

Comparison of Mild-Reaction versus Anaphylactic Hazelnut-Apple Patients

In the hazelnut-apple group, sensitization to LTP and PR10-proteins did not differ significantly between patients with anaphylactic and mild symptoms (for LTP 2/6 vs. 2/12, $p = 0.57$ and for PR10-proteins 5/6 vs. 11/12, $p = 1.00$) (fig. 1).

We further compared sIgE levels for PR10-proteins of the hazelnut-only and apple-only group versus the hazelnut-apple group, irrespective of the clinical severity. Remarkably, the median IgE-levels of the hazelnut-only group were lower than the hazelnut-apple group (Bet v 1, 0.24 vs. 44.2, $p < 0.001$; Pru p 1, 0.08 vs. 21.0, $p < 0.001$; Cor a 1, 0.36 vs. 40.5, $p < 0.001$; Mal d 1, 0.30 vs. 9.6, $p < 0.001$).

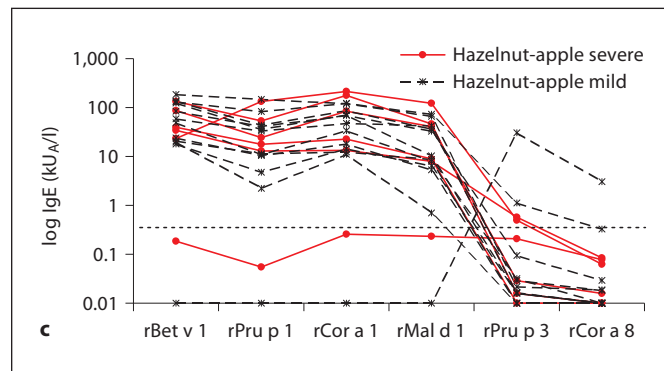
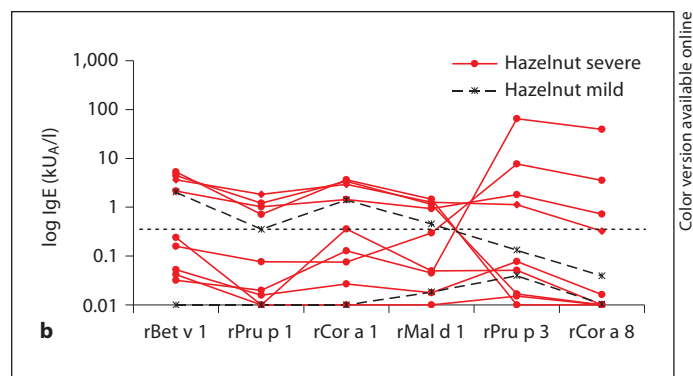
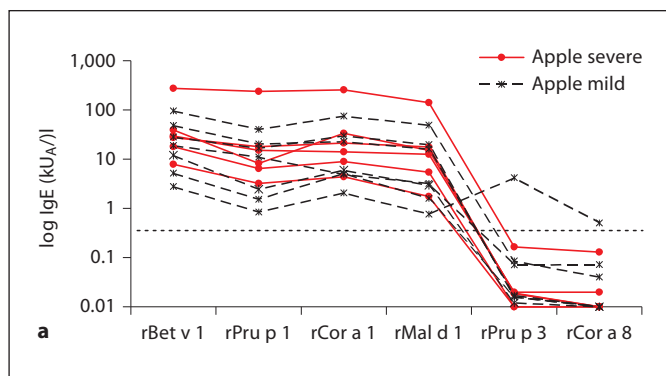


Fig. 2. Sensitization pattern in patients with apple-only (a), hazelnut-only (b) and combined hazelnut-apple allergy (c). Dotted lines indicate a cut off value of 0.35 kU_A/l.

0.001, respectively), whereas the median IgE levels in the apple-only group did not differ from the hazelnut-apple group (Bet v 1, 27.5 vs. 44.2; Pru p 1 11.0 vs. 21.0; Cor a 1 14.0 vs. 40.5; Mal d 1 12.5 vs. 9.6, all *p* values >0.05). We did not perform comparisons between these groups for LTP, as the median sIgE was <0.35.

Sensitization Patterns in Apple-Only, Hazelnut-Only and Hazelnut-Apple Patients

The combined sensitization patterns to LTP and PR10-proteins were further studied in the 3 subgroups (fig. 2). In the apple-only group, all except for one of the patients (both anaphylactic and mildly allergic) were sensitized to PR10-proteins but not to LTP (fig. 2a). In contrast, hazelnut-only patients did not display such a homogenous sensitization pattern: some were sensitized both to PR10-proteins and hazelnut LTP Cor a 8 (1/11). Others were sensitized to only Cor a 8 (2/11) or PR10-proteins (5/11) and others to neither of these (3/11) (fig. 2b). However, in the hazelnut-apple group, the LTP and PR10-proteins recognition pattern was similar to that of the apple-only patients (fig. 2c). Only 1 hazelnut-apple patient differed from the others, by recognizing LTP but not PR10-proteins (fig. 2c).

Discussion

Previous studies showed that apple as well as hazelnut allergy in northern and central Europe is mainly mild and Bet v 1-associated [3, 5–7]. However, in this study, we show that anaphylaxis to apple and hazelnut also occurs in a birch-endemic area and that different sensitization patterns for PR10-proteins and LTP are seen. Anaphylactic apple-allergic patients are only sensitized to PR10-proteins and not to LTP. In anaphylactic hazelnut-allergic patients, the observed pattern is more diverse, with sensitization to: PR10-proteins only, LTP only, both PR10-proteins and LTP or neither PR10-proteins or LTP.

So far, recognition of LTP by IgE of adult apple-allergic and hazelnut-allergic patients was mainly found in the Mediterranean area and was related to having severe symptoms [3–7]. Sensitization to LTP is rarely reported in anaphylactic hazelnut-allergic or apple-allergic patients from birch-endemic areas, but this might be due to the low number of such patients being included in the previous studies (Hansen et al. [3] *n* = 1, Pastorello et al. [7] *n* = 0, Schocker et al. [5] *n* = 1, Fernandez-Rivas et al. [6] *n* = 1). Although we included the largest population of patients with anaphylaxis to hazelnut and/or apple so far

from a birch-endemic area, our study population was small. This all serves to indicate that anaphylactic reactions to hazelnut and apple are not frequently seen in birch-endemic areas. In our centre, 9 out of 187 hazelnut-allergic patients had an anaphylactic reaction solely to hazelnut and for apple this was 6 out of 241. In a previous study in children from a birch-endemic area, we found that hazelnut LTP sensitization was associated with having more severe symptoms [13]. We now show that LTP sensitization also occurs in adults from a birch-endemic area with anaphylaxis to hazelnut allergy, but not in those with anaphylaxis to apple.

Although LTP sensitization (Mal d 3 and Cor a 8) leads to a higher risk of severe reactions, sensitization to these allergens can also be detected in patients with a mild food allergy. Hansen et al. [3] demonstrated sensitization to Cor a 8 in 71% of patients with severe symptoms to hazelnut and in 21% of patients with milder reactions. For apple allergy, Fernandez-Rivas et al. [6] showed that 95/131 patients with a higher than median level of Mal d 3 had a local reaction. In our study, 3/21 (14.3%) patients with mild symptoms recognized LTP.

The aim of our study was to compare the sensitization to PR10-proteins and LTP in patients with mild and anaphylactic reactions. However, some hazelnut-allergic patients with anaphylaxis in our study did not recognize either PR10-proteins or LTP. These patients, but also the patients who did recognize these allergens, may be sensitized to other hazelnut allergens that were not measured, such as Cor a 14 (2S albumin), Cor a 11 (7S globulin) or Cor a 9 (11S globulin), the latter has been related to severe hazelnut allergy [17, 18]. For apple, four allergens have been identified to date according to the guideline of the International Union of Immunological Societies Allergen Nomenclature Subcommittee (www.allergen.org): Mal d 1 (PR10-protein), Mal d 2 (thaumatin like protein), Mal d 3 (LTP) and Mal d 4 (profilin). The allergen sensitization profile for these four allergens was previously investigated across Europe [6]. That study showed that apple allergy in northern and central Europe was mild and related to birch pollinosis and sensitization to Mal d 1, whereas in Spain apple allergy was frequently severe and related to peach allergy and sensitization to Mal d 3 (apple LTP). In our study, apple LTP, Mal d 3 was not measured because it was not available. However, a previous study showed that Pru p 3, which we analyzed, shares common epitopes with Mal d 3 and can well be used as a replacement [19]. Other studies support the close similarity and cross-reactivity between Mal d 3 and Pru p 3 [6, 20–22]. The reason why some patients from our study sensitized

to PR10-proteins develop mild reactions and others develop anaphylactic reactions has to be further elucidated. Patient-related (e.g. age, asthma, medication, recent infection and general health) and event-related factors (allergen dose, food matrix, food form i.e. raw/cooked, season, exercise and alcohol) may play a role as well [23].

Food allergy can result from primary sensitization to inhalant allergens or to the food itself (i.e. the oral route). Worthy of note, in our study, sensitization to PR10-proteins was lower in the hazelnut-only group than in the hazelnut-apple group. Furthermore, in the hazelnut-only group there were hardly any patients with mild symptoms ($n = 2$). Together, these findings may indicate that sensitization to hazelnut (even in a birch-endemic region) is not always pollen-related and may be associated with severe symptoms.

In conclusion, this is the first study to show that the sensitization profile to PR10-proteins and LTP in anaphylactic patients from a birch-endemic area differs between different plant foods (i.e. hazelnut and apple). With regard to LTP, anaphylaxis to hazelnut in a birch-endemic area can be LTP-associated, whereas anaphylaxis to apple is not. Since some anaphylactic patients did not recognize either PR-10 proteins nor LTP, other allergens may play a role.

Acknowledgement

We would like to thank Anita Kober (Research and Development, Phadia AB, Uppsala, Sweden) for providing and performing the ImmunoCAPs.

References

- 1 Zuberbier T, Edenharter G, Worm M, Ehlers I, Reimann S, Hantke T, Roehr CC, Bergmann KE, Niggemann B: Prevalence of adverse reactions to food in Germany – a population study. *Allergy* 2004;59:338–345.
- 2 Osterballe M, Hansen TK, Mortz CG, Host A, Bindslev-Jensen C: The prevalence of food hypersensitivity in an unselected population of children and adults. *Pediatr Allergy Immunol* 2005;16:567–573.
- 3 Hansen KS, Ballmer-Weber BK, Sastre J, Lidholm J, Andersson K, Oberhofer H, Lluch-Bernal M, Ostling J, Mattsson L, Schocker F, Vieths S, Poulsen LK: Component-resolved in vitro diagnosis of hazelnut allergy in Europe. *J Allergy Clin Immunol* 2009;123:1134–1141.

- 4 Schocker F, Luttkopf D, Scheurer S, Petersen A, Cistero-Bahima A, Enrique E, San Miguel-Moncin M, Akkerdaas J, van RR, Vieths S, Becker WM: Recombinant lipid transfer protein Cor a 8 from hazelnut: a new tool for in vitro diagnosis of potentially severe hazelnut allergy. *J Allergy Clin Immunol* 2004;113:141–147.
- 5 Schocker F, Luttkopf D, Muller U, Thomas P, Vieths S, Becker WM: IgE binding to unique hazelnut allergens: identification of non-pollen-related and heat-stable hazelnut allergens eliciting severe allergic reactions. *Eur J Nutr* 2000;39:172–180.
- 6 Fernandez-Rivas M, Bolhaar S, Gonzalez-Mancebo E, Asero R, van LA, Bohle B, Ma Y, Ebner C, Rigby N, Sancho AI, Miles S, Zuidmeer L, Knulst A, Breiteneder H, Mills C, Hoffmann-Sommergruber K, van RR: Apple allergy across Europe: how allergen sensitization profiles determine the clinical expression of allergies to plant foods. *J Allergy Clin Immunol* 2006;118:481–488.
- 7 Pastorello EA, Vieths S, Pravettoni V, Farioli L, Trambaioli C, Fortunato D, Luttkopf D, Calamari M, Ansaloni R, Scibilia J, Ballmer-Weber BK, Poulsen LK, Wutrich B, Hansen KS, Robino AM, Ortolani C, Conti A: Identification of hazelnut major allergens in sensitive patients with positive double-blind, placebo-controlled food challenge results. *J Allergy Clin Immunol* 2002;109:563–570.
- 8 Schimek EM, Zwolfer B, Briza P, Jahn-Schmid B, Vogel L, Vieths S, Ebner C, Bohle B: Gastrointestinal digestion of Bet v 1-homologous food allergens destroys their mediator-releasing, but not T cell-activating, capacity. *J Allergy Clin Immunol* 2005;116:1327–1333.
- 9 Ortolani C, Ispano M, Pastorello E, Bigi A, Ansaloni R: The oral allergy syndrome. *Ann Allergy* 1988;61:47–52.
- 10 Pastorello EA, Farioli L, Pravettoni V, Ortolani C, Ispano M, Monza M, Baroglio C, Scibola E, Ansaloni R, Incorvaia C, Conti A: The major allergen of peach (*Prunus persica*) is a lipid transfer protein. *J Allergy Clin Immunol* 1999;103:520–526.
- 11 Brenna O, Pompei C, Ortolani C, Pravettoni V, Farioli L, Pastorello EA: Technological processes to decrease the allergenicity of peach juice and nectar. *J Agric Food Chem* 2000;48:493–497.
- 12 Asero R, Mistrello G, Roncarolo D, de Vries SC, Gautier MF, Ciurana CL, Verbeek E, Mohammadi T, Knul-Brettlova V, Akkerdaas JH, Bulder I, Aalberse RC, van RR: Lipid transfer protein: a pan-allergen in plant-derived foods that is highly resistant to pepsin digestion. *Int Arch Allergy Immunol* 2001;124:67–69.
- 13 Flinterman AE, Akkerdaas JH, den Hartog Jager CF, Rigby NM, Fernandez-Rivas M, Hoekstra MO, Buijnzeel-Koomen CA, Knulst AC, van RR, Pasmans SG: Lipid transfer protein-linked hazelnut allergy in children from a non-Mediterranean birch-endemic area. *J Allergy Clin Immunol* 2008;121:423–428.
- 14 Gaier S, Oberhuber C, Hemmer W, Radauer C, Rigby NM, Marsh JT, Mills CE, Shewry PR, Hoffmann-Sommergruber K: Pru p 3 as a marker for symptom severity for patients with peach allergy in a birch pollen environment. *J Allergy Clin Immunol* 2009;124:166–167.
- 15 Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, Brown SG, Camargo CA Jr, Cydulka R, Galli SJ, Gidudu J, Gruchalla RS, Harlor AD Jr, Hepner DL, Lewis LM, Lieberman PL, Metcalfe DD, O'Connor R, Muraro A, Rudman A, Schmitt C, Scherrer D, Simons FE, Thomas S, Wood JP, Decker WW: Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117:391–397.
- 16 Dreborg S: Skin tests in the diagnosis of food allergy. *Pediatr Allergy Immunol* 1995;6(suppl 8):38–43.
- 17 Beyer K, Grishina G, Bardina L, Grishin A, Sampson HA: Identification of an 11S globulin as a major hazelnut food allergen in hazelnut-induced systemic reactions. *J Allergy Clin Immunol* 2002;110:517–523.
- 18 Garino C, Zuidmeer L, Marsh J, Lovegrove A, Morati M, Versteeg S, Schilte P, Shewry P, Arlorio M, van RR: Isolation, cloning, and characterization of the 2S albumin: a new allergen from hazelnut. *Mol Nutr Food Res* 2010;54:1257–1265.
- 19 Borges JP, Barre A, Culerrier R, Granier C, Didier A, Rouge P: Lipid transfer proteins from Rosaceae fruits share consensus epitopes responsible for their IgE-binding cross-reactivity. *Biochem Biophys Res Commun* 2008;365:685–690.
- 20 Asero R, Mistrello G, Roncarolo D, de Vries SC, Gautier MF, Ciurana CL, Verbeek E, Mohammadi T, Knul-Brettlova V, Akkerdaas JH, Bulder I, Aalberse RC, van RR: Lipid transfer protein: a pan-allergen in plant-derived foods that is highly resistant to pepsin digestion. *Int Arch Allergy Immunol* 2000;122:20–32.
- 21 Sanchez-Monge R, Lombardero M, Garcia-Selles FJ, Barber D, Salcedo G: Lipid-transfer proteins are relevant allergens in fruit allergy. *J Allergy Clin Immunol* 1999;103:514–519.
- 22 Diaz-Perales A, Garcia-Casado G, Sanchez-Monge R, Garcia-Selles FJ, Barber D, Salcedo G: cDNA cloning and heterologous expression of the major allergens from peach and apple belonging to the lipid-transfer protein family. *Clin Exp Allergy* 2002;32:87–92.
- 23 Hourihane JO, Knulst AC: Thresholds of allergenic proteins in foods. *Toxicol Appl Pharmacol* 2005;207:152–156.