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Food allergy to apple, peach and celery in atopic dermatitis patients, analysis of sensitisation to molecular components

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ABSTRACT

Aim: To evaluate the occurrence of food allergy to peach/apple/celery in atopic dermatitis patients and to analyse the sensitisation to molecular components.

Methods: The diagnosis of food allergy was confirmed according to the results of the challenge test/history and according to the examination of the sensitisation to molecular components with Multiplex ISAC testing.

Results and conclusion: Altogether 113 atopic dermatitis patients were examined – 54 men, 59 women, the average age 39.9 years. Allergy to apple was confirmed in 18 patients (15.9%), to peach in 17 patients (15.1%), to celery in 6 patients (5.3%). The sensitisation to Bet v 1 (Birch, PR 10 protein) was confirmed in 64 patients (56.7%) included in the study. From the whole number of patients with sensitisation to Bet v 1, we confirmed in 42.2% food allergy and in 48.4% food sensitisation to apple/peach/celery.

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Introduction

Plant food, especially fruits and vegetables, is part of a healthy diet and their consumption is recommended for prevention of cardiovascular and metabolic disorders. However, in predisposed individuals, food-allergic reactions are caused/induced upon uptake of a range of fruits and vegetables. While the range of allergenic fruits is broad, the majority of frequent inducers of allergic reactions belong to the Rosaceae family (Matricardi et al., 2016). The Rosaceae family includes many edible fruits; apple, cherry, and peach are the best-studied species from an allergy point of view (Matricardi et al., 2016). The allergens identified in the fruits of the Rosaceae family are (1) PR-10 proteins (Bet v 1 family member), (2) profilin, (3) non-specific Lipid transfer proteins type 1, 2 (nsLTP) and (4) thaumatin-like protein. Additionally in peach a gibberellin-regulated protein has been detected (Matricardi et al., 2016). Atopic dermatitis (AD) is a chronic intermittent inflammatory skin disease that may be associated with food allergies; the prevalence of

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IgE-mediated food allergy among children with AD is about 35% (Matricardi et al., 2016; Soares-Weiser et al., 2014; Flammarion et al., 2011; King et al., 2009). Other numerous trigger factors for AD have been identified, including inhalable respiratory allergens, irritative substances and infectious microorganisms, such as *Staphylococcus aureus* (Matricardi et al., 2016). There are only rare studies dealing with the question of food allergy in adult patients suffering from atopic dermatitis. Over the past decade, a significant increase in the prevalence of food allergy-related anaphylaxis indicates that there is a rise in food allergy (Matricardi et al., 2016; Soares-Weiser et al., 2014; Flammarion et al., 2011; King et al., 2009). Adolescent and adult patients can acquire food allergy via primary sensitization to inhalant allergens on the basis of cross-reactivity between proteins in inhalant sources and in food (Matricardi et al., 2016). Pollen from Fagales trees are one of the most frequent causes of winter/spring respiratory allergy in the temperate areas of the Northern Hemisphere. This order includes two main families (Betulaceae and Fagaceae) comprising different trees characterized by a rather limited number of homologous, cross-reacting allergens (Matricardi et al., 2016). Generally, three different clinical patterns are described after ingesting of food allergens: (a) immediate type symptoms such as erythema, angioedema, urticaria, but no eczema, bronchial, gastrointestinal or cardiovascular symptoms of anaphylaxis, which appear within minutes up to two hours after ingesting the relevant food; (b) isolated, eczematous, late-type reactions, which normally appear as flare-ups of typical eczematous lesions occurring within hours to two days after ingestion and (c) combined reaction pattern of non-eczematous, immediate type reactions and eczematous, late-type reactions (Matricardi et al., 2016). Clinical practice guidelines covering general diagnosis and management of food allergies have recently been published by the EAACI Food Allergy Diagnosis Systematic Review and Guidelines (Matricardi et al., 2016; Soares-Weiser et al., 2014; Flammarion et al., 2011; King et al., 2009). Progress in laboratory diagnostics of IgE-mediated allergy is the use of component-resolved diagnosis (CRD) or molecular diagnosis (MD) of allergies (Matricardi et al., 2016). This approach has been developed when highly purified or recombinant allergen molecules have become available. These molecules are the allergenic proteins toward which the specific and clinically relevant IgE immune response is directed. Molecular diagnosis provides a major step in improving the accuracy of diagnosing IgE-mediated sensitizations in food allergy. The ability to identify and characterize single allergens at a molecular level has added a significant body of understanding as to the mechanism of sensitization to foods (Matricardi et al., 2016; Luengo & Cardona, 2014). The introduction of allergen molecules has had a major effect on analytic specificity and allergy diagnosis. They are used in both singleplex ImmunoCAP and multiplex ImmunoCAP ISAC assays. The major advantage of ISAC is the comprehensive IgE pattern obtained with a minute amount of serum (van Hage et al., 2017; Melioli et al., 2011; Jakob et al., 2015; Kleine-Tebbe & Jakob, 2015). ImmunoCAP ISAC (Thermo Fisher), based on 112 different molecular components (both extracted and recombinant), is the most studied and most frequently used molecular diagnostic tool based on a microarray (van Hage et al., 2017; Melioli et al., 2011; Jakob et al., 2015; Kleine-Tebbe & Jakob, 2015). To date limited components are available to facilitate the in vitro diagnosis in fruit and vegetable allergies (Fernandez-Rivas et al., 2006). This comprises cross-reactive allergens derived from inhalant allergenic sources (Bet v 1 and Bet v 2 from birch pollen and the latex allergens Hev b 6.01, 6.02, and 11) as well as food components

from few Rosaceae fruits (Mal d 1, 3; Pru p 1, 3, 4), kiwifruit allergens (Act d 1, 2, 5, 8) and some Apiaceae allergens (Dau c 1, Api g 1), (Fern_andez-Rivas et al., 2006, Boyano-Mart_inez et al., 2013a, 2013b, Ballmer-Weber et al., 2000; Ballmer-Weber & Hoffmann-Sommergruber, 2011). Allergies to fruits and vegetables are often initiated by a primary sensitization to pollen. As the majority of fruit and vegetable allergens are part of few protein families and characterized by a high cross-reactivity, the clinical relevance of a sensitization needs to be often established by food challenges (Matricardi et al., 2016). Overview of the molecular components per protein families for the apple/peach/celery allergens is recorded in Table 1.

Table 1. Molecular components in apple, peach and celery allergens (Fern_andez-Rivas et al., 2006, Boyano-Mart_inez et al., 2013a, 2013b, Ballmer-Weber et al., 2000, Bauermeister et al., 2009, Pastorello et al., 2013). Molecular components in ISAC Multiplex testing are shown extra bold*. BP – birch pollen, GP – grass pollen.

Allergen	Allergenicity	Risk factor	Sensitisation rate
Mal d 1* Pathogenesis-related protein PR-10	High in BP allergic patients	Birch pollen, Bet v 1 related sensitisation	15%–70% of apple allergic patients (Fern_andez-Rivas et al., 2006)
Mal d 2 Thaumatin-like protein	Minor allergens in ripening fruits and are upregulated upon biotic and abiotic stress	Consumption of raw and processed fruits	5%–18% of apple allergic patients (Fern_andez-Rivas et al., 2006)
Mal d 3 nsLTP type 1	High in southern Europe		1%–50% of apple allergic patients (Fern_andez-Rivas et al., 2006)
Mal d 4 Profilin	GP and BP allergic patients	Grass pollen, profilin related sensitisation	10%–40% of apple allergic patients (Fern_andez-Rivas et al., 2006)
Pru p 1* Pathogenesis-related protein PR-10	High in BP allergic patients	Birch pollen, Bet v 1 related sensitisation	11% in Spanish peach allergic children 7%–31% in adults (Boyano-Mart_inez et al., 2013a, 2013b, Pastorello et al., 2013)
Pru p 3* nsLTP type 1	High in southern Europe	Consumption of raw and processed fruits	96% in peach allergic children 62%–96% peach allergic adults (Boyano-Mart_inez et al., 2013, Pastorello et al., 2013)
Pru p 4 Profilin	GP allergic patients	Consumption of fruits	10% in peach allergic children 7%–34% adults (Boyano-Mart_inez et al., 2013, Pastorello et al., 2013)
Pru p 7 Gibberellin-regulated protein	A small protein upregulated upon biotic stress and located in the peach peel		
Api g 1* Pathogenesis-related protein PR-10	High in BP allergic patients	Birch pollen, Bet v 1 related sensitisation	75% (Ballmer-Weber et al., 2000, Bauermeister et al., 2009)
Api g 2 nsLTP type 1	it is expressed in the stalks		
Api g 4 Profilin	BP allergy		42% (Ballmer-Weber et al., 2000, Bauermeister et al., 2009)
Api g 5 FAD-containing oxidase	the carbohydrate moieties of this enzyme seem to be relevant for the IgE-binding capacity		45% (Ballmer-Weber et al., 2000, Bauermeister et al., 2009)
Api g 6 nsLTP type 2	it is found in the tuber		

In our previous studies, we evaluated the occurrence of sensitisation to food and inhalant allergens in patients suffering from AD. The diagnostic work-up should comprise not only the laboratory methods, but also the diagnostic hypoallergenic diet and the challenge test in patients with suspected food allergy (Čelakovská et al., 2015; Čelakovská & Bukač, 2011; Čelakovská & Bukač, 2017).

Method

Patients and methods

In the period of 2018–2020, 113 patients suffering from atopic dermatitis at the age of 14 years and older were examined. All these patients were examined in the Department of Dermatology, Faculty Hospital Hradec Králové, Charles University, Czech Republic. The diagnosis of atopic dermatitis was made with the Hanifin-Rajka criteria (Hanifin & Rajka, 1980). Exclusion criteria were systemic therapy (cyclosporin, systemic corticoids, biological therapy), pregnancy, breastfeeding. Patients with atopic dermatitis having other systemic diseases were excluded from the study as well. Complete dermatological and allergological examination was performed in all patients included in the study. This study was approved by Ethics committee of Faculty Hospital Hradec Králové, Charles University of Prague, Czech Republic.

Examination of specific IgE to molecular components

The serum level of the sIgE was measured by the component-resolved diagnosis microarray-based sIgE detection assay ImmunoCAP ISAC (Phadia, Thermo Fisher Scientific, Uppsala, Sweden). ImmunoCAP ISAC is a solid-phase multiple immunoassay which enables to determine 112 different components from 51 allergen sources (van Hage et al., 2017; Melioli et al., 2011). The allergens are applied in triplicates to ensure the test reproducibility. The specific IgE values are presented in arbitrary units called ISAC Standardized Units (measuring range of 0.3–100 ISU-E). The level of specific IgE higher than 0.3 ISU-E was assessed as positive. The level of molecular components in ISU-E was evaluated: < 0.3 – negative, 0.3–0.9 low positivity, 0.9–15 moderate positivity, above 15 ISU-E very high positivity (van Hage et al., 2017; Melioli et al., 2011).

Scoring of AD

Severity of atopic dermatitis was scored in agreement with SCORAD (Scoring of atopic dermatitis) with the assessment of topography items (affected skin area), intensity criteria and subjective parameters. The severity of atopic dermatitis was evaluated with SCORAD as a mild form to 25 points, as moderate over 25–50 points, as a severe form over 50 points (Zuidmeer et al., 2008). This examination was performed during one year every two month and the average SCORAD index was calculated (European Task Force on Atopic Dermatitis, 1993).

Anamnestic data

A detailed personal history of possible food allergy was taken for all included patients. The patients indicate whether they suffer from immediate or late food reactions affecting the skin, gastrointestinal tract, or respiratory tract, not only after the ingestion of apple/celery/peach, but also after ingestion of other foods. We recorded previous reactions to apple/celery/peach, symptoms, affected organ system, onset and course, cofactors (exercise, NSAID, alcohol). The open exposure test was not performed in patients with the early reaction after the ingestion of apple/celery/peach in their history because of anaphylactic reaction danger. All of these patients have been carefully examined and they are always monitored.

Confirmation of food allergy

- (1) The diagnosis of apple/celery/peach allergy was confirmed according to convincing history with the clinical reaction after apple/celery/peach ingestion or according to the challenge test and according to the positive results to molecular components in ISAC Multiplex testing.
- (2) Sensitisation to apple/celery/peach was confirmed in patients with positive results in ISAC Multiplex testing and with no clinical reaction after ingestion of apple/celery/peach.

The elimination diet

In patients without previous history about apple/celery/peach allergy we recommended the elimination diet with the elimination of suspected food allergens for the period of 5 weeks (Čelakovská et al., 2015; Čelakovská & Bukač, 2011; Čelakovská & Bukač, 2017).

Open exposure test

Open exposure test was performed after this diet in intervals without symptoms or during a consistent period with regard to atopic dermatitis (not in pollen season in patients with pollen allergy). In generally, the open exposure test (OET) was recommended to perform with three doses of examined foods given during two days.

One dose of examined food was given in incremental dosages in 10 min intervals during one hour. Apple and peach were served in the form of fresh fruit in a gradually increasing dose, celery was heat treated.

The food challenge results was scored as positive if one or more of the following objective and subjective clinical reactions were noted: itching, rash, urticaria, angioedema, vomiting, wheezing, abdominal pain, diarrhoea, pruritus, or worsening of atopic dermatitis. Early reactions were defined as clinical symptoms within 2 h after the ingestion of food and late symptoms if occurring after more than 2 h. In the case the physician or the patient recorded worsening of the atopic dermatitis or some other reactions during the open exposure test, the patient continued in the elimination of suspected food and the severity of atopic dermatitis was evaluated every 2 month during 1 year. If the open exposure test was negative, the patient introduced this food in the diet regimen. The severity of atopic dermatitis was evaluated during the ingestion of food over a period

of 2 months during 1 year. If there is a suspicion to food allergy to more than one food, the next open exposure test was performed in 2–3 weeks after the first exposure test (Čelakovská et al., 2015; Čelakovská & Bukač, 2011; Čelakovská & Bukač, 2017).

Statistical analysis

We analysed the results of specific IgE to molecular components Mal d 1, Pru p 1, Pru p 3, Api g 1, Bet v 1 and the results of the history/challenge test. Venn diagrams were used to show this analysis.

Control group

When introducing the test into the clinical examination, we also examined 15 healthy volunteers – blood donors (equivalent to age, male and female representation). All of these blood donors had in the multiplex examination (ISAC Multiplex testing) the specific IgE negative.

Results

Patients

We included 113 patients suffering from atopic dermatitis in the study; 54 men and 59 women with the average age of 39.9 years and with the average SCORAD 39 points (s.d.13.5 points). The mild form of AD was recorded in 15 patients (13.3%), moderate form in 67 patients (59.3%), severe form in 31 patients (27.4%); 63 patients (55.8%) suffer from asthma bronchiale and 85 patients (75.2%) suffer from rhinitis. The positive history/challenge test after ingestion of peach were recorded in 21 patients (18.6%), of apple in 23 patients (20.3%), of celery in 24 patients (21.2%). The positive results to molecular components of peach (Pru p 1, Pru p 3) were recorded in 54 patients (47.8%), to molecular component of apple (Mal d 1) in 53 patients (46.9%) and to molecular component of celery (Api g 1) in 25 patients (22.1%). The characteristics of patients is shown in Table 2.

The results of the examination of specific IgE to molecular components of apple/celery/peach in patients with clinical reactions in history/challenge tests are recorded in Table 3. In 21 patients (= 100%) with clinical reaction to peach, the positivity to at

Table 2. The characteristic of patients with atopic dermatitis.

– 113 patients examined: 54 men, 59 women, the average age 39.9 years, min. age 14 years, max. age 67 years
– the average SCORAD 39 points, s.d. 13.5 points
– the severity of AD – number of patients: mild form 15 (13.3%), moderate form 67 (59.3%), severe form 31 (27.4%)
– number of patients with asthma bronchiale – 63 (55.8%), number of patients with allergic rhinitis – 85 (75.2%)
– the positive history/challenge test:
peach 21 patients (18.6%)
apple 23 patients (20.3%)
celery 24 patients (21.2%)
– the positive results to molecular components:
peach (Pru p 1 and/or Pru p 3) – 54 patients (47.8%)
apple (Mal d 1) – 53 patients (46.9%)
celery (Api g 1) – 25 patients (22.1%)

Table 3. Patients with positive history/challenge test to peach (21 patients = 100%), celery (24 patients = 100%), apple (23 patients = 100%) – the results of specific IgE to molecular components of peach/celery/apple in ISAC Multiplex testing.

Number of patients with positive history/challenge test	Specific IgE to molecular components – number of patients with positive and negative results	
	Positive results to at least to one of molecular components – food allergy confirmed	Negative results to molecular components
Peach 21 = 100%	17 (80.1%)	4 (19.1%)
Celery 24 = 100%	6 (25.0%)	18 (75.0%)
Apple 23 = 100%	18 (78.3%)	5 (21.8%)

least to one of molecular components of peach (Pru p 1, Pru p 3) was recorded in 17 patients (80.1%), the negative results were recorded in 4 patients (19.1%). In 24 patients (= 100%) with clinical reaction to celery, the positivity to molecular component of celery Api g 1 was recorded in 6 patients (25.0%), the negative results were recorded in 18 patients (75.0%). In 23 patients (= 100%) with clinical reaction to apple, the positivity to molecular component of apple Mal d 1 was recorded in 18 patients (78.2%), the negative results were recorded in 5 patients (21.8%), [Table 3](#).

The clinical reactions to apple/peach/celery in patients with positive challenge test/history are recorded in [Table 4](#). From these patients, majority of them suffer from oral allergy syndrome (83.4% – 91.3%), pruritus was observed in more than half of these patients (56.5% – 62.5%), gastrointestinal symptoms were present in 20.9% of patients with clinical reaction to celery, in 43.5% of patients with clinical reaction to apple and in 23.8% of patients with reaction to peach. Urticaria was present in 12.5% of patients with reaction to celery, in 17.4% of patients with reaction to apple and in 38.1% of patients with reaction to peach. Worsening of breathing was observed only in 1 patient (1.35%) with reaction to celery. Regarding the worsening of atopic dermatitis, the new eczematous lesions as the late reactions appeared in 20.9% of patients with reaction to celery, in 34.8% of patients with reaction to apple and in 38.1% of patients with reaction to peach.

Table 4. Positive history/challenge test and the kind of clinical reaction in 113 patients included in the study (oral allergy syndrome, pruritus, gastrointestinal symptoms, worsening of atopic dermatitis, urticaria, worsening of breathing). The ratio of patients with different kind of clinical reaction is calculated from the number of patients suffering from clinical reactions to celery (24 patients = 100%), to apple (23 patients = 100%) and to peach (21 patients = 100%) also.

Food allergens	Number of patients with positive history/challenge test (from 113 patients in the study)	Clinical symptoms					
		OAS	Pruritus	GIT symptoms	Worsening of eczema	Urticaria	Worsening of breathing
Celery	24 (21.2%)	20(17.6) %	15(13.3)%	5(4.5)%	5(4.5)%	3(2.7)%	1 (1.35)%
	24 = 100%	83.4%	62.5%	20.9%	20.9%	12.5%	4.1%
Apple	23 (20.1%)	21 (18.6)%	13(11.5)%	10(8.9)%	8(7.1)%	4(3.5)	0%
	23 = 100%	91.3%	56.5%	43.5%	34.8%	17.4%	0%
Peach	21 (18.6%)	18 (15.9)%	12(10.7)%	5(4.4)%	8(7.1)%	3(2.7)%	0%
	21 = 100%	85.7%	57.1%	23.8%	38.1%	14.3%	0%

OAS = oral allergy syndrome, GIT = gastrointestinal symptoms.

Table 5. Analysis of sensitisation to molecular components of celery/apple/ peach in 113 atopic dermatitis patients (113 patients = 100%). The positive results to molecular components of celery/ apple/ peach:

- (1) in the whole group of 113 patients
- (2) in patients suffering from clinical reaction to celery/apple/ peach (food allergy confirmed)
- (3) in patients without clinical reaction to celery/apple/ peach (sensitisation)

Molecular component	Allergen, protein family	Number of patients with positive results to molecular components of peach		
		1) Number of positive results in the whole group of 113 patients	2) Clinical reaction yes - number of patients - food allergy confirmed	3) Clinical reaction no - number of patients - sensitisation confirmed
Pru p 1	Peach, PR 10 protein	51 (45.1%)	16 (14.2%)	35 (30.9%)
Pru p 3	Peach, nsLTP	11 (9.7%)	4 (3.6%)	7 (6.2%)
	Total number of patients	54 (47.8%)	17 (15.1%)	37 (32.7%)
Mal d 1	Apple, PR 10 protein	54* (= 100%)	17 (31.5%)	37 (68.5%)
		53 (46.9%)	18 (15.9%)	35 (30.9%)
Api g 1	Celery, PR 10 protein	53** (= 100%)	18 (33.9%)	35 (66.1%)
		25 (22.1%)	6 (5.3%)	19 (16.8%)
		25*** (= 100%)	6 (24.0%)	19 (76%)

* The positive results to one or more of molecular components of peach were recorded altogether in 54 patients from 113 patients (47.8%); in these patients (54 patients = 100%), the clinical reactions to peach were recorded in 17 patients (31.5%), no clinical reactions to peach were recorded in 37 patients (68.5%).

**The positive results to molecular component of apple are recorded altogether in 53 patients from 113 patients (46.9%); in these patients (53 patients = 100%), the clinical reactions to apple were recorded in 18 patients (33.9%), no clinical reactions to apple were recorded in 35 patients (66.1%).

***The positive results to molecular component of celery are recorded altogether in 25 patients from 113 patients (22.1%); in these patients (25 patients = 100%), the clinical reactions to celery were recorded in 6 patients (24.0%), no clinical reactions to celery were recorded in 19 patients (76.0%).

In Table 5, we show the positive results to molecular components of peach, apple and celery: (1) in the whole group of 113 patients, (2) in patients with positive history/challenge test to apple/celery/peach, (3) in patients without positive history/challenge test to apple/celery/peach (= sensitisation). The diagnosis of food allergy was confirmed in patients with positive results in the open exposure test/history and with the positive results to molecular components at the same time. The food allergy to peach was confirmed altogether in 17 patients (15.1%), to apple in 18 patients (15.9%), to celery in 6 patients (5.3%). We show the Venn diagram (areas proportional to frequencies) of positive results to molecular components in patients suffering from peach allergy – **Diagram 1** and in patients suffering from sensitisation to peach (patients with positive results to molecular components of peach with no clinical reaction) – **Diagram 2**.

The sensitisation to Bet v 1 was confirmed in 64 patients from 113 patients included in the study (= 56.7%). These patients suffer from food allergy to apple/peach/celery in 42.2%. In another 48.4% of patients with sensitisation to Bet v 1 we recorded positivity to molecular components of apple/peach/celery with no clinical reaction (Table 6). We show the Venn diagrams (areas proportional to frequencies) of patients suffering from food allergy to apple/ peach/celery (**Diagram 3**) and from food sensitisation to apple/ peach/celery (**Diagram 4**) in the whole group of patients with positivity to Bet v 1.

The levels of specific IgE to molecular components of examined food allergens in ISAC Multiplex testing in ISU –E are recorded in Table 7. We show the levels of

Table 6. Sensitisation to Bet v 1 (64 patients (=100%) and the ratio of patients, who suffer from allergy (sensitisation) to apple/peach/celery. FA* – food allergy confirmed with clinical reaction and positive results to molecular components of food allergens. Sensitisation** – no clinical reaction to food allergens, but positive results to molecular components of food allergens.

Food allergen	Bet v 1 sensitisation – 64 patients = 100%			
	Number of patients with FA*		Number of patients with food sensitisation**	
Apple	18	28.1%	35	54.7%
Celery	6	9.3%	19	29.7%
Peach	17	26.6%	37	57.8%
Total number of patients	27	42.2%	31	48.4%

Table 7. The levels of specific IgE to molecular components of examined food allergens in ISAC Multiplex testing in ISU –E. (1) in the whole group of 113 patients (= 100%). (2) in patients with confirmed food allergy (FA). (3) in patients without confirmed FA, with only sensitisation.

Molecular component	Number of patients with positive results to molecular components					
	(1) the whole group of patients (113 patients = 100%)		(2) FA yes		(3) FA no (sensitisation only)	
	number of patients	mean level of specific IgE	number of patients	mean level of specific IgE	number of patients	mean level of specific IgE
rApig1*	25 (22.1%)	6.72	6 (5.3%)	8.8	19 (16.8%)	5.94
rMald1*	53 (46.9%)	16.95	18 (15.9%)	19.49	35 (30.9%)	15.64
rPrup1*	51 (45.1%)	11.197	16 (14.2%)	9.6	35 (30.9%)	11.53

Table 8. Number of patients with confirmed multiple food allergy (sensitisation) to apple and/or peach and/or celery.

Allergen	FA	Sensitisation
Peach + Apple	9 (7.9%)	27 (23.9%)
Celery+ Peach+ Apple	1 (0.8%)	13 (11.5%)

FA = positive results to molecular components, positive history/challenge test.

Sensitisation = positive results to molecular components, negative history/challenge test.

specific IgE (1) in the whole group of 113 patients (= 100%), (2) in patients with confirmed food allergy (FA), (3) in patients without confirmed FA, with only sensitisation. There is no difference in the level of specific IgE to molecular components in patients with food allergy to apple/peach/celery and in patients with food sensitisation (positive results to molecular components with no clinical reactions).

Number of patients with confirmed multiple food allergies (sensitisation) is recorded in Table 8. The food allergy to peach and apple was confirmed in 9 patients (7.9%) at the same time. The food allergy to celery, peach and apple was confirmed in 1 patient (0.8 %) at the same time. The sensitisation to celery, peach and apple was confirmed at the same time in 13 patients (11.5%), the sensitisation to apple and peach was confirmed in 27 patients (23.9%).

Discussion

Despite their clinical importance in atopic dermatitis patients, apple/peach/celery allergy epidemiology remains understudied in this group of patients. In our study, we confirmed the occurrence of apple/peach/celery allergy according to the challenge test/history and

according to the examination with molecular components. There are few studies dealing with this question in adolescents and adults suffering from atopic dermatitis according to the databases in Medline, Pubmed, and Web of Science. Although we found some studies dealing with the examination of molecular components in atopic dermatitis patients, we did not find any similar one going to the detailed description of the results with molecular components. Molecular allergy diagnosis is a typical method of precision medicine (van Hage et al., 2017; Melioli et al., 2011) and it enhances the specificity of IgE-diagnosis in polysensitized respiratory allergies, can be applied in food allergies and atopic dermatitis (van Hage et al., 2017; Melioli et al., 2011).

In our study, the food allergy to apple was confirmed in 15.9%, to celery in 5.3%, and to peach in 15.1% of patients. Majority of these patients suffer from oral allergy syndrome; pruritus was observed in more than half of these patients, followed by urticaria and gastrointestinal symptoms (nausea, abdominal pain) and only in a rare case we recorded worsening of breathing. Regarding the worsening of atopic dermatitis, the new eczematous lesions as the late reactions appeared in 20.9% of patients with reaction to celery, in 34.8% of patients with reaction to apple, and in 38.1% of patients with reaction to peach. On the other hand, no positive results in ISAC Multiplex testing were recorded in some patients with positive history/challenge test. According to this ratio, we could calculate the sensitivity of molecular components in ISAC Multiplex testing (sensitivity is calculated as proportion of positive IgE antibody tests in patients with confirmed food allergy). But we don't use this terminology because it would remind us of its connection with making a decision. We are more interested in the role of species – specific and cross reactive molecular components in patients suffering from food allergy. According to these ratios, the sensitivity of Api g 1 is 25%, of Mal d 1 it is 78.3%, of Pru p 1 it is 80.1%; Api g 1, Mal d 1 and Pru p 1 are mainly cross reactive components PR 10 Proteins. The PR-10 proteins are actually one of the 11 subfamilies of the Bet v 1 family. PR-10 proteins are expressed in high concentrations in reproductive tissues such as pollen, seeds, and fruits. Many birch pollen-allergic patients show allergic reactions to various fruits and vegetables, which are caused by IgE cross-reactivity between Bet v 1 and homologous allergens from plant foods. Most Bet v 1-related food allergens have been found in members of certain plant families: Rosaceae (apple, pear, stone fruits), Apiaceae (celery, carrot), and Fabaceae (soybean, peanut), (Matricardi et al., 2016; Fernandez-Rivas et al., 2006; Boyano-Martinez et al., 2013a, 2013b; Ballmer-Weber et al., 2000). We show the relation between the occurrence of allergy (sensitisation) to apple/peach/celery and the sensitisation to molecular component Bet v 1 in our study also. The sensitisation to Bet v 1 (Birch, PR 10 protein) was confirmed in 64 patients (56.7%) included in the study. From the whole number of patients with sensitisation to Bet v 1, we confirmed in 42.2% food allergy and in 48.4% food sensitisation to apple/peach/celery.

In celery, the PR-10 protein is a major allergen, especially in Central Europe. Also, profilin is supposed to sensitize a relevant number of celeriac-allergic patients (Ballmer-Weber et al., 2000; Bublin et al., 2003). In the recent past, non-specific lipid transfer proteins (nsLTPs) have been identified from celery. While the nsLTP type 1 is expressed in the stalks, the nsLTP type 2 is found in the tuber (Ballmer-Weber et al., 2000; Gadermaier et al., 2011; Vejvar et al., 2013). Only limited IgE cross-reactivity is observed between those two different proteins (Matricardi et al., 2016; Ballmer-Weber

et al., 2000; Bublin et al., 2003; Gadermaier et al., 2011; Vejvar et al., 2013). Non-specific lipid transfer proteins have been suggested to mediate the transfer of phospholipids between vesicles and membranes. However, plants have used the three-dimensional scaffold of the nsLTPs in various ways and many nsLTPs play a role in plant defense against fungi and bacteria. Allergenic nsLTPs are a large group of proteins that are resistant to heat and digestion (Egger et al., 2010). Non – specific LTPs are found in high concentrations in epidermal tissues of fruits. They are major allergens of fruits from the Rosaceae family. In addition, allergenic nsLTPs are present in nuts, seeds, vegetables, and *Hevea brasiliensis* latex. Besides their presence in plant foods, nsLTPs are also expressed in pollen of weeds, olive, and plane. Rosacea fruit nsLTP include Mal d 3 from apple and Pru p 3 from peach (Matricardi et al., 2016; Fernandez-Rivas et al., 2006; Boyano-Martínez et al., 2013a, 2013b). In our study, we examined the sensitization to Mal d 1, Pru p 1 (PR 10 protein) and to Pru p 3 (nsLTP) and we confirmed, that majority of patients suffering from peach allergy have positive results to Pru p 1; the food allergy to peach with the positive results to Pru p 1 was confirmed in 14.2% of patients included in the study, on the other hand the food allergy to peach with the positivity to Pru p 3 was confirmed in 3.6% of patients included in the study.

In the systematic review the overall prevalence of food allergies caused by vegetables is around 1.4% (Zuidmeer et al., 2008). The sensitization rates for vegetables were assessed by Burney et al. within the ECRHS study. Sensitization to carrot was determined of 3.6% and increased in 2014–5.0% while celeriac sensitization was observed in 3.5% and 6.3% of the general population, respectively (Burney et al., 2010; Burney et al., 2014). In celeriac allergy allergen-specific sensitization prevalence was investigated within the EuroPrevall project (Bauermeister et al., 2009). For carrot allergy, one study investigated the sensitization rate in Switzerland, Denmark, and Spain (Ballmer-Weber et al., 2012). To date limited components are available to facilitate the in vitro diagnosis in fruit and vegetable allergies (Ballmer-Weber & Hoffmann-Sommergruber, 2011). This comprises cross-reactive allergens derived from inhalant allergenic sources (Bet v 1 and Bet v 2 from birch pollen and the latex allergens Hev b 6.01, 6.02, and 11) as well as food components from few Rosaceae fruits (Mal d 1, 3; Pru p 1, 3, 4), kiwifruit allergens (Act d 1, 2, 5, 8) and some Apiaceae allergens (Dau c 1, Api g 1), (Boyano-Martínez et al., 2013a, 2013b; Ballmer-Weber et al., 2000).

Prevalence data for plant-food allergies are scarce and the available data so far originate from a few studies. In a systematic review by Zuidmeer et al. (Zuidmeer et al., 2008), the overall prevalence for fruits ranged from 0.1% to 4.3%. Within a European Community Respiratory Health Survey (ECRHS) overall sensitization rates for fruits were assessed by Burney and colleagues in 2010 and 2014. Peach was the most frequent inducer of sensitization increasing from 5.4% to 7.9% in 2014. Apple ranked second with a sensitization rate of 4.2% and 6.5% followed by kiwifruit with 3.6% and 5.2% sensitizing capacity (Burney et al., 2010; Burney et al., 2014). Prevalence data on allergen-specific sensitization have been generated by a few European wide studies. For apple the SAFE study provided data on Mal d 1–Mal d 4 (Fernandez-Rivas et al., 2006), while the peach allergens were investigated in Spanish and Italian studies (Boyano-Martínez et al., 2013a, 2013b; Pastorello et al., 2013) reflecting the clear-cut difference in the frequency of LTP sensitization predominant in the southern European areas as compared to the PR-10 sensitization detected in areas with Fagales pollen exposure. Several

kiwifruit studies were performed including a multicenter, within the Euro-Prevall project and single centre studies (Bublin et al., 2011; Le et al., 2013).

The sensitization pattern to these allergens is geographically influenced. Sensitization rates to the Bet v 1 homologous proteins are significantly higher in countries with high pollen exposure of the Fagales trees (birch, alder, hazel), whereas sensitization to nsLTP is significantly higher in Mediterranean countries (Fernandez-Rivas et al., 2006; Burney et al., 2014). Sensitization to Rosaceae fruit profilins is more evenly distributed but most likely higher in the Mediterranean area (Fernandez-Rivas et al., 2006). Knowledge on sensitization to Thaumatin-like fruit proteins or gibberellin-regulated protein is restricted. The Bet v 1-related food proteins, the profilin, and the nsLTP are panallergens, depicting a high cross-reactivity across the plant kingdom and sensitization to these molecules is often not accompanied by clinical symptoms (Gonzalez-Mancebo et al., 2011; Lidholm et al., 2006).

In a prospective cohort study with an open study design, it was examined whether tolerance development in “apple allergy sufferers” can be achieved through regular consumption of low-allergen apples. For this purpose, the expression of oral symptoms after eating a fruit of the variety “Golden Delicious” before and after daily consumption of an allergen-poor apple for 90 days was examined. The subjects showed significantly less symptoms when eating the “Golden Delicious” after regular consumption of the low-allergen apples of old varieties. It appears possible to achieve an oral tolerance to highly allergenic apples through regular consumption of old varieties with the allergen content (Bergmann et al., 2020).

Asero et al. detected the risk factors for systemic reactions induced by labile food allergens. A retrospective multicenter study was performed on patients with a documented history of systemic allergic reaction to labile plant food allergens and on age-matched controls with a history of oral allergy syndrome (OAS) induced by the same foods. Offending foods, their amount, and state (solid or liquid), and potential cofactors (nonsteroidal anti-inflammatory drugs, protonic pump inhibitors – PPI, exercise, alcohol, and fasting) were considered. According to their results, PR – 10 proteins and profilin – induced systemic reactions are facilitated by PPI, ingestion of large amounts of unprocessed foods, and fasting. Soybean beverages represent a risk for PR – 10 hypersensitive patients and should be avoided (Asero et al., 2020).

Pollen food Syndrome (PFS) to *Rosaceae* fruits and soybean, related to Bet v 1 homologue sensitization has been reported increasingly throughout Japan, possibly due to the wide distribution of alder. The authors Mari Sasaki et al. analysed the prevalence, demographic and clinical characteristics of children with oral symptoms to *Rosaceae* fruits/soybean; defined as oral symptoms occurring shortly after ingesting apple, peach, cherry or soybean. According to their results, oral symptoms to *Rosaceae* fruits/soybean, which is suggestive of PFS was reported by 1%–3% Japanese school children. It was associated with the geographic alder sensitization rate, supporting the underlying sensitization to Bet v 1 (Sasaki et al., 2020).

Another study provides an immunologic explanation of why secondary food allergy cannot be effectively treated by administration of the sensitizing pollen allergen. The authors found that treatment with Bet v 1 promotes specific IgG antibodies that cross-react with Mal d 1 but lack sufficient affinity to induce cross-protection. The latter finding may be the result of very few differing amino acid residues in the epitope of

cross-reactive allergens, as previously demonstrated for an IgE-blocking IgG4 mAb isolated from an AIT-treated individual.

On the other hand, treatment with the secondary food allergen induced a food allergen-specific de novo antibody response that is characterized by IgG1 antibodies with IgE-blocking bioactivity and specific for epitopes exclusive of the apple allergen. Finally, the authors demonstrated for the first time that allergen-specific IgG1 antibodies are the dominant protective blocking subclass in the early phase of allergy treatment (Sánchez Acosta et al., 2020 Oct).

In this manuscript, we evaluate only the food allergy to apple, peach and celery, because these foods are commonly represented in the diet. Although the range of allergenic fruits is broad, the majority of frequent inducers of allergic reactions belong to the Rosaceae family. Another reason why we focus on these foods, such as apple, peach and celery, is that we can compare the results of the exposure test with the results of specific IgE to molecular components in ISAC Multiplex testing. This Multiplex ISAC testing enables the examination of specific IgE to other molecular components from different kinds of foods, such as peanuts, hazelnuts, cashew nuts and Brazil nuts, walnuts, sesame seed, soybean, wheat, cod, shrimp, cow's milk, egg white and egg yolk, kiwi. In our previous publications, we evaluated the food allergy to other food allergens (Čelakovská et al., 2020; Čelakovská et al., 2021; Čelakovská et al., 2021).

According to our results we confirmed the high occurrence of food allergy to apple and peach in atopic dermatitis patients. Although the main symptoms of food allergy is the oral allergy syndrome, in some of patients we can observe cutaneous manifestations of food allergy with pruritus and worsening of atopic dermatitis also. Almost all patients suffering from food allergy to apple and peach are sensitised to Bet v 1 molecular components. On the other hand, we can expect occurrence of food allergy to apple/peach/celery in 42.2% of patients with positivity to molecular component Bet v 1.

Allergy screening with the ISAC multiplex allergen array not only with a similar fidelity leads to allergy diagnosis, but is favourable in polysensitized patients, in small children with limited skin area, but higher strain, in elderly when skin tests get less reliable (Matricardi et al., 2016; Melioli et al., 2011), in all settings of inflamed or atopic skin and when medications interfering with skin prick testing cannot be discontinued. ISAC testing has a high sensitivity and specificity (Panzner et al., 2014), and showed a strong correlation with singleplex tests including IgE and skin prick testing with extracts, specifically for respiratory allergens with slight alterations from allergen to allergen (Huss-Marp et al., 2015; Williams et al., 2016; Ahlgrim et al., 2015; Jung et al., 2015).

Conclusion

In atopic dermatitis patients, allergy to apple was confirmed in 15.9%, to peach in 15.1%, to celery in 5.3% of patients. The sensitisation to molecular components with no clinical reactions to peach/apple/celery was confirmed in 32.7%/ 31.9%/ 16.8% of patients.

Atopic dermatitis patients are sensitized to Bet v 1 in 56.7%; in these patients we confirmed the occurrence of food allergy to apple/peach/celery in 42.2% and the sensitisation to apple/peach/celery in 48.4%. The majority of patients with clinical reaction to apple/peach/celery suffer from oral allergy syndrome; pruritus was observed in more than half of these patients, followed by urticaria and gastrointestinal symptoms

(nausea, abdominal pain) and only in a rare case we recorded worsening of breathing. The new eczematic lesions as the late reactions appeared in 20.9% of patients with reaction to celery, in 34.8% of patients with reaction to apple and in 38.1% of patients with reaction to peach. Molecular allergy diagnosis improves the risk evaluation, sorts out genuine from cross-reactive sensitizations, improves the overall predictive value of the diagnostic results, as well as the accuracy of the resulting allergen immunotherapy.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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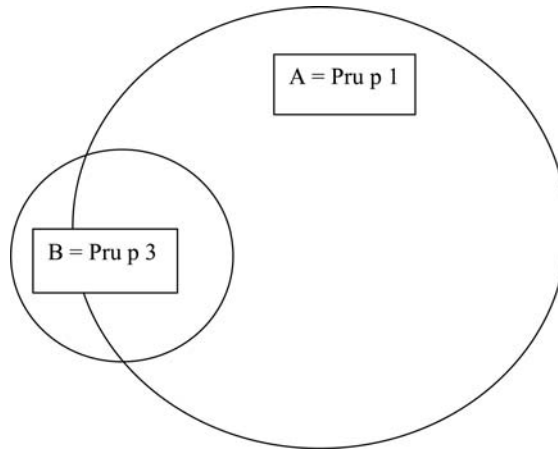
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Appendix

Diagram 1. Venn diagram (areas proportional to frequencies) of positive results to molecular components in patients suffering from food allergy to peach – altogether 17 patients (15.1%) – positive results to molecular components with positive challenge test/history.



Letters A to B represent:

A – 13 (11.5%) patients with positive results to Pru *p* 1

3 (2.6%) patients with positive results to Pru *p* 3 and Pru *p* 1

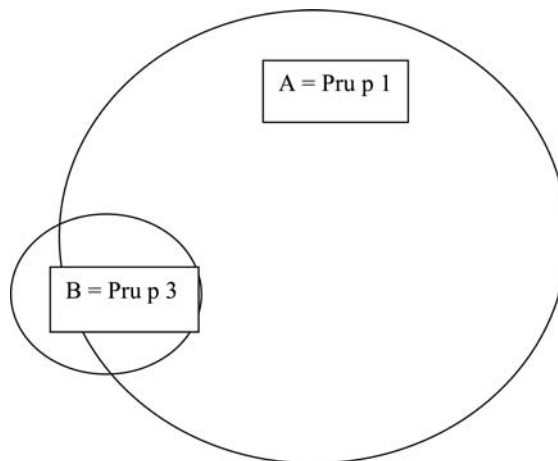
altogether 16 patients (14.2%)

B – 3 (2.6%) patients with the positive results to Pru *p* 3 and Pru *p* 1

1(0.9%) patient with positivity only to Pru *p* 3

altogether 4 patients (3.5%)

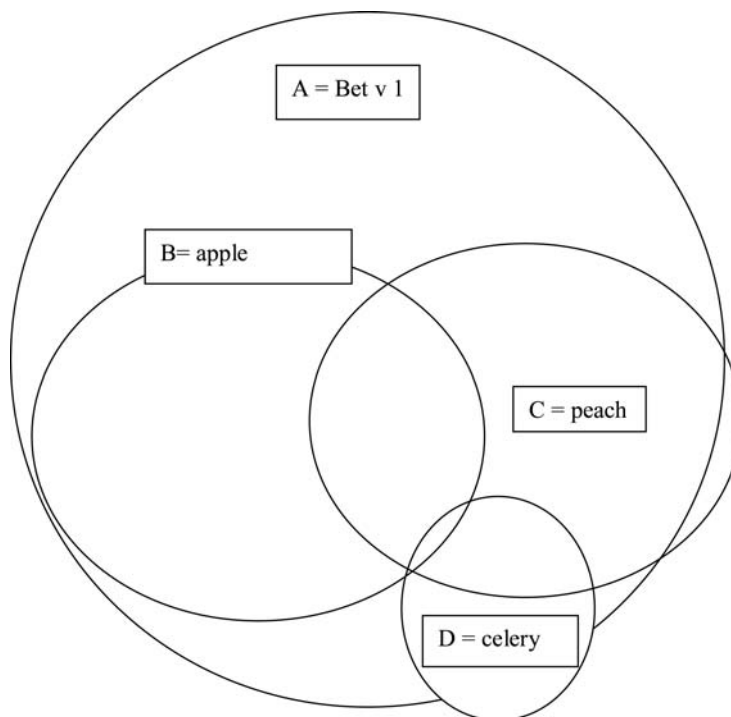
Diagram 2. Venn diagram (areas proportional to frequencies) of positive results to molecular components in patients suffering from sensitisation to peach – altogether 37 (32.7%) patients with positive results to molecular components with no clinical reaction.



Letters A to B represent:

- A – 30 (26.5%) patients with positive results to Pru *p* 1
 5 (4.4%) patients with positive results to Pru *p* 3 and Pru *p* 1
altogether 35 patients (30.9%)
 B – 5 (4.4%) patients with the positive results to Pru *p* 3 and Pru *p* 1
 2 (1.8%) patients with positivity only to Pru *p* 3
altogether 7 patients (6.2%)

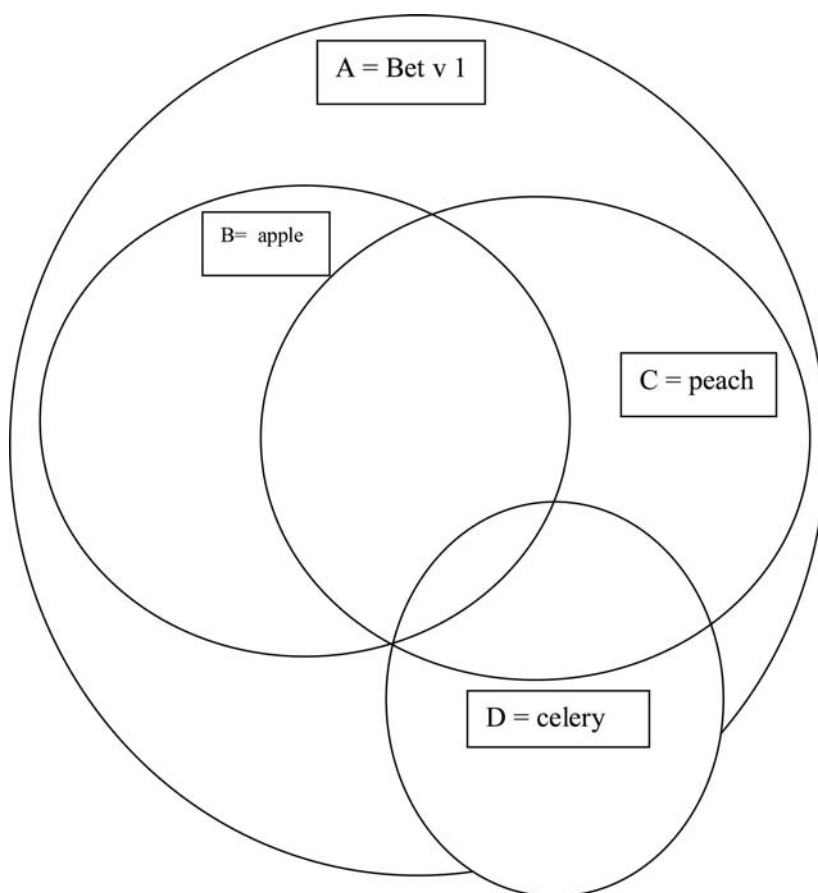
Diagram 3. Venn diagram (areas proportional to frequencies). Sensitisation to Bet v 1 (64 patients - 56.7%) in relation to patients with food allergy to apple/peach/celery.



Letters A to D represent:

- A – 64 patients (56.7%) with sensitisation to Bet v 1**
B – altogether 18 (15.9%) patients with confirmed food allergy to apple
 - 9 (7.9%) patients with food allergy to peach only
 - 1 (0.9%) patient with allergy to celery, apple and peach
 - 8 (7.1%) patients with food allergy to peach and apple
C – altogether 17 (15.1%) patients with food confirmed food allergy to peach
 - 8 (7.1%) patients with food allergy to apple and peach,
 - 1 (0.9%) patient with food allergy to celery, apple and peach
 - 8 (7.1%) patients with allergy to peach only, the sensitisation to Bet v 1 was not confirmed in 1 (0.9%) patient with allergy to peach
D – altogether 6 (5.3%) patients with confirmed food allergy to celery
 - 1 (0.9%) patient with food allergy to celery, apple and peach
 - 2 (1.8%) patients with allergy to peach and celery
 - 4 (3.6%) patients with allergy to celery only, the sensitisation to Bet v 1 was not confirmed in 1 (0.9%) patient with allergy to celery

Diagram 4. Venn diagram (areas proportional to frequencies). Sensitisation to Bet v 1 (64 patients – 56.7%) in relation to patients with food sensitisation to apple/peach/celery.



A – 64 (56.7%) patients with sensitisation to Bet v 1

B – altogether 35 (30.9%) patients with sensitisation to apple

- 13 (11.5%) patients with sensitisation to apple + peach + celery
- 14 (12.4%) patients with sensitisation to apple + peach
- 8 (7.1%) patients with sensitisation to apple only

C – altogether 37 (32.7%) patients with sensitisation to peach

- 13 (11.5%) patients with sensitisation to apple + peach + celery
- 14 (12.4%) patients with sensitisation to apple + peach
- 10 (8.8%) patients with sensitisation to peach only

D – altogether 19 (16.8%) patients with sensitisation to celery

- 13 (11.5%) patients with sensitisation to apple + peach + celery
- 3 (2.7%) patients with sensitisation to celery + peach
- 3 (2.7%) patients with sensitisation to celery only, the sensitisation to Bet v 1 was not confirmed in 1 (0.9%) patient with sensitisation to celery