

BRIEF COMMUNICATION

Birch pollen sensitization with cross-reactivity to food allergens predominates in adults with eosinophilic esophagitis

B. D. van Rhijn¹, R. van Ree^{2,3}, S. A. Versteeg², B. J. Vlieg-Boerstra⁴, A. B. Sprickelman⁴, I. Terreehorst³, A. J. P. M. Smout¹ & A. J. Bredenoord¹

¹Department of Gastroenterology & Hepatology, Academic Medical Center, University of Amsterdam; ²Department of Experimental Immunology, Academic Medical Center, University of Amsterdam; ³Department of Otorhinolaryngology, Academic Medical Center, University of Amsterdam; ⁴Department of Respiratory Medicine and Allergy, Emma Children's Hospital, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands

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Correspondence

A. J. Bredenoord, MD, PhD, Department of Gastroenterology & Hepatology, Academic Medical Center, Amsterdam, PO Box 22660, 1100 DD Amsterdam, the Netherlands.

Tel.: +31 20 566 17 45

Fax: +31 20 691 70 33

E-mail: a.j.bredenoord@amc.uva.nl

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Abstract

EoE patients show variable sensitization patterns to food and aeroallergens. The value of allergy testing in adult EoE patients is unclear. Component-resolved diagnosis (CRD) may offer additional insights into sensitization patterns. The aim of this study was to characterize sensitization patterns in adult EoE patients using CRD. Serum from 76 patients (17 female), age 38.6 ± 1.5 years, was analyzed for reactivity to 112 different allergen components using an immuno-solid-phase allergen chip (ISAC). We observed any sensitization in 59 patients (78%), of which 54 patients were polysensitized. Aeroallergen sensitization, mostly against components of grass or tree pollen, or house dust mite, was observed in 74% of the patients. Birch pollen (rBet v 1) sensitization with cross-reactivity to food allergen components was observed in 30 patients (39%). In conclusion, food sensitizations in EoE patients are mainly caused by cross-reactivity to food allergens after primary birch pollen sensitization. Pollen and food sensitizations may cause or maintain esophageal inflammation in EoE patients. CRD provides more insight into sensitization patterns, identifies additional food allergen sensitizations and might be useful to direct dietary therapy in EoE.

Studies using skin prick tests and atopy patch tests in adult eosinophilic esophagitis (EoE) patients show variable sensitization patterns to food and aeroallergens (1–6). The value of allergy testing as a means to direct dietary therapy in EoE patients is under debate (7, 8). Compared to SPT and APT, serum immunoglobulin (Ig)E CAP testing increases detection of food allergens in pediatric EoE (9). However, with all these tests, only a limited number of allergens can be tested, and sensitivity and specificity are often low (10). Protein microarrays have recently been introduced as promising tools for the simultaneous assessment of specific IgE antibodies against multiple recombinant or purified natural allergen components in serum, enabling component-resolved diagnostics (CRD). CRD has shown good analytical performance compared to serum IgE CAP testing (11). It enables discrimination between primary sensitization and cross-reactivity to allergens and provides patient-tailored results, and its microarray format enables testing for a large number of allergens.

We hypothesized that CRD may offer additional insight into the sensitization patterns in EoE and aimed to characterize sensitization patterns in adult EoE patients using CRD.

Methods

Adults clinicopathologically diagnosed with EoE, visiting the outpatient clinic of the Gastroenterology Department of the Academic Medical Center, Amsterdam, the Netherlands, between October 2011 and April 2013, were consecutively enrolled, regardless of their atopic status (12). The study was approved by the medical ethics committee of our institution. At home, patients filled out a questionnaire evaluating the presence of atopic disorders and dysphagia in their personal or family history. All patients underwent vena puncture to obtain serum samples. Using ImmunoCAP ISAC, specific IgE antibodies against 112 different food and aeroallergen components were measured according to the manufacturer's

recommendations (Phadia AB [at present Thermo Fisher Scientific] Uppsala, Sweden). Data are expressed as mean $\pm$ SEM.

Results

Patient characteristics

We included 76 adult EoE patients, aged 38.6 ± 1.5 years, 59 (78%) male. Atopic characteristics are summarized in Table 1. Most patients (84%) reported at least one atopic disease in their medical history. Symptoms suggestive of oral allergy syndrome were reported by 28 patients (37%). One of the patients reported a history of systemic symptoms after peanut exposure. Current symptoms of dysphagia were reported by 95% of the patients, whereas 5% reported no current symptoms of dysphagia. A seasonal pattern in the presence of dysphagia was reported by 3% of the patients; no seasonal pattern in the degree of dysphagia was reported.

Sensitization patterns

Sensitizations to 80 different components were found in 59 patients (78%) (Table 2). Five patients were monosensitized (1 to rBet v 1, 1 to nCyn d 1, 1 to nGly m 5, and 2 to rVes v 5), and 54 patients were polysensitized. Sensitization to more than one aeroallergen or food allergen was observed in 57 patients (75%). Patients were predominantly sensitized to molecules present in grass pollen, tree pollen, and house dust mite (Table 2). In total, 494 sensitizations to aeroallergens were found in 56 patients (74%), with 8.8 ± 0.6 (range 1–22) sensitizations on average.

We observed cross-reactivity to 3.7 ± 0.4 (range 1–9) food allergen components in 30 patients (39% of all patients). All

of these 30 patients were sensitized to birch pollen (rBet v 1), and cross-reactivity occurred via PR-10 proteins to hazelnut (27/30), apple (23/30), peach (19/30), peanut (16/30), soybean (11/30), kiwifruit (2/30), and celery (4/30). Eight patients (11%) were sensitized to profilin proteins.

Furthermore, in 17 patients (22%), sensitizations to food components capable of causing systemic reactions were found. In total, we observed 31 primary sensitizations to 21 components of 11 different food allergens in these patients, with a mean of 1.8 ± 0.4 (range 1–6) per sensitized patient. Patients were sensitized to hazelnut (rCor a 8), peach (rPru p 3), peanut (rAra h 1/2/3/6/9), soybean (nGly m 5), walnut (nJug r 1/2/3), cow's milk (nBos d 4/5/8/lactoferrin), kiwifruit (nAct d 2/5), buckwheat (nFag E 2), egg white (nGal d 1), cod (rGad c 1), and shrimp (nPen m 1).

CRD vs history

Food allergen sensitization assessed by CRD was not related to acute dysphagia after ingestion of that certain food. Symptoms suggestive of food allergies (oral allergy symptoms, anaphylaxis, eczema after food intake) were reported by 39 patients (Table 3). In 12 (31%) of these patients, sensitization against food allergens was not confirmed with CRD, while in 21 (54%) of these patients, sensitization was confirmed by CRD. In 20 (51%) of the patients reporting food allergies, additional unreported sensitizations were identified by CRD. Absence of food allergies was reported by 37 patients and confirmed in 28 (76%) of these patients. In 9 (24%) of those 37 patients, we observed sensitization to one or more food allergen components. In total, in 29 (38%) of all 76 patients, sensitizations to 3.0 ± 0.4 (range 1–9) additional food allergen components were found.

Discussion

In this study, using CRD, we have identified sensitization to birch pollen with cross-reactivity to food allergens as the dominant food allergen sensitization pattern in the majority of adult EoE patients. We also found a high rate of polysensitization to food and aeroallergens.

We confirm the widespread aeroallergen sensitizations to grass and tree pollen, house dust mite, and cat/dog (2, 4, 7, 13). Sensitization to food allergens in EoE patients has been suggested to be a result of aeroallergen inhalation, although most studies have not provided detailed information about the interplay between both (1, 2, 7). As CRD identifies sensitization to specific components of allergens, we were able to study sensitization patterns in more detail. We demonstrate that the majority of EoE patients is sensitized to aeroallergens and that most food allergen sensitizations are a result of cross-reactivity, as recently described by Simon et al. in a smaller cohort (13). Whereas these authors demonstrated a dominant pattern of cross-reactivity to profilins, in our cohort cross-sensitization was predominantly directed against food allergens containing PR-10 proteins, due to primary birch pollen sensitization.

PR-10 proteins are present in birch pollen, fruits, and nuts. These proteins share a high degree of structural

Table 1 Atopic characteristics of EoE patients

Atopy	N (%)
Any atopic disease	64 (84.2)
Asthma	28 (36.8)
Allergic rhinitis	52 (68.4)
Atopic dermatitis	24 (31.6)
Food allergy	38 (50.0)
Atopic family history	56 (73.7)
Asthma	26 (34.2)
Allergic rhinitis	45 (59.2)
Atopic dermatitis	15 (19.7)
Food allergy	17 (22.4)
Sensitization patterns (CRD)	N (%)
Sensitized patients	59 (77.6)
Monosensitized	5 (6.6)
Polysensitized	54 (71.1)
Aeroallergens	56 (73.7)
Food allergens	36 (47.4)
Primary food allergen sensitization	17 (22.4)
Cross-reactivity to food allergens	30 (39.5)

Table 2 Sensitization patterns in adult EoE patients

Allergen	Molecules	Patients, N (%)	Allergen	Molecules	Patients, N (%)
<i>Aeroallergens</i>			<i>Aeroallergens</i>		
Grass pollen		40 (52.6)	Mite		34 (44.7)
Bermuda grass	nCyn d 1	31 (40.8)	House dust mite	rBlo t 5	2 (2.6)
Timothy grass	rPhl p 1	37 (48.7)		nDer f 1	22 (28.9)
	rPhl p 2	16 (21.1)		rDer f 2	27 (35.5)
	nPhl p 4	20 (26.3)		nDer p 1	22 (28.9)
	rPhl p 5	26 (34.2)		rDer p 2	27 (35.5)
	rPhl p 6	12 (15.8)		rDer p 10	1 (1.3)
	rPhl p 7	1 (1.3)	Storage mite	rLep d 2	6 (7.9)
	rPhl p 11	12 (15.8)	<i>Food allergens</i>		
	rPhl p 12	6 (7.8)	Apple	rMal d 1*	23 (30.3)
Tree pollen		39 (51.3)	Hazelnut	rCor a 1.0401*	27 (35.5)
Alder	rAln g 1	23 (30.3)		rCor a 8†	1 (1.3)
Birch	rBet v 1	32 (42.1)	Peach	rPru p 1*	19 (25.0)
	rBet v 2	6 (7.8)		rPru p 3†	2 (2.6)
	rBet v 4	1 (1.3)	Peanut	rAra h 1‡	1 (1.3)
Hazel pollen	rCor a 1.0101	20 (26.3)		rAra h 2‡	2 (2.6)
Japanese cedar	nCry j 1	1 (1.3)		rAra h 3‡	1 (1.3)
Cypress	nCup a 1	3 (3.9)		rAra h 6‡	2 (2.6)
Olive	nOle e 1	13 (17.1)		rAra h 8*	16 (21.1)
	nOle e 7	2 (2.6)		rAra h 9†	1 (1.3)
Plane tree	nPla a 2	6 (7.9)	Soybean	rGly m 4*	11 (14.5)
	nPla a 3	1 (1.3)		nGly m 5‡	1 (1.3)
Weed pollen		9 (11.8)	Walnut	nJug r 1‡	1 (1.3)
Mugwort	nArt v 1	2 (2.6)		nJug r 2‡	5 (6.6)
	nArt v 3	1 (1.3)		nJug r 3†	2 (2.6)
Goosefoot	rChe a 1	2 (2.6)	Cow's milk	nBos d 4	2 (2.6)
Annual mercury	rMer a 1	6 (7.9)		nBos d 5	2 (2.6)
Wall pellitory	rPar j 2	2 (2.6)		nBos d 8	1 (1.3)
Animal		29 (38.2)		nBos d lactoferrin	1 (1.3)
Dog	rCan f 1	12 (15.8)	Kiwi	nAct d 2	3 (3.9)
	rCan f 2	6 (7.9)		nAct d 5	1 (1.3)
	nCan f 3	4 (5.3)		nAct d 8*	2 (2.6)
	rCan f 5	7 (9.2)	Celery	rApi g 1*	4 (5.3)
Horse	rEqu c 1	6 (7.9)	Buckwheat	nFag e 2‡	1 (1.3)
	rEqu c 3	3 (3.9)	Egg white	nGal d 1	1 (1.3)
Cat	rFel d 1	23 (30.3)	Cod	rGad c 1§	1 (1.3)
	nFel d 2	5 (6.6)	Shrimp	nPen m 1¶	1 (1.3)
	rFel d 4	7 (9.2)	Cockroach	nBla g 7	1 (1.3)
Mouse	nMus m 1	7 (9.2)	<i>Other</i>		
Mold		10 (13.2)	Common wasp	rVes v 5	5 (6.6)
Alternaria	rAlt a 1	7 (9.2)	Paper wasp	rPol d 5	1 (1.3)
Aspergillus	rAsp f 1	2 (2.6)	Anisakis	rAni s 3¶	1 (1.3)
	rAsp f 3	3 (3.9)	Latex	rHev b 6.01	1 (1.3)
				rHev b 8**	6 (7.9)
			CCD	nMUXF3	1 (1.3)

*Allergens containing PR-10 proteins (Bet v 1-homologues); †PR-14 proteins (nonspecific lipid transfer proteins); ‡Storage proteins; §Parvalbumin; ¶Tropomyosin; **Profilin; PR-10 and profilin proteins are sensitive to heat and digestion, whereas PR-14 proteins, storage proteins, parvalbumin, and tropomyosin are stable to heat and digestion and often cause systemic reactions.

homology, and their size is approximately 17 kD (14). We have recently shown that molecules more than twice this size can pass the esophageal mucosa of EoE patients due to an impaired esophageal barrier (15). Another important characteristic of PR-10 proteins is that they are digested by pepsin (14). PR-10 proteins may thus activate the immune system in the esophagus, but will be

degraded upon arrival in the stomach. This might be the reason why eosinophilic inflammation is limited to the esophagus.

A strength of this study is that CRD provides more detailed insights into the sensitization patterns in EoE. Furthermore, we demonstrate that CRD identifies additional food allergen sensitizations not known to the patient. A limitation of this

Table 3 Self-reported food allergies vs food allergen sensitizations observed with Component-resolved diagnosis (CRD) in adult EoE patients

Patient ID	Age, years	Sex	Self-reported food allergens	Sensitization pattern (CRD)		Patient query vs CRD		
				Primary food allergens, often causing systemic reaction	Cross-reactive food allergens	Self-reported food allergens confirmed by CRD, N	Self-reported food allergens confirmed by CRD, N	Additional food allergen sensitizations by CRD, N
1	32	M	Shellfish	–	–	1	0	0
2	46	M	Almond, apple, cherry, pear, walnut	Walnut	Hazelnut, apple, peach, soybean, peanut, kiwifruit, celery	3	2	6
3	29	F	–	–	Hazelnut, apple, peach, soybean, peanut, kiwifruit	n.a.	n.a.	6
4	40	M	–	–	–	n.a.	n.a.	0
5	60	M	–	–	–	n.a.	n.a.	0
6	22	M	Blackberry, egg, peanut, raspberry	–	–	4	0	0
7	35	F	Mussels	–	–	1	0	0
8	23	M	Apple, nuts, peanut	–	Hazelnut, apple, peach, peanut	0	3	1
9	74	M	–	–	–	n.a.	n.a.	0
10	21	F	Fruit, nuts, peanut	Walnut	Peach	1	2	0
11	50	M	Apple, nuts, peanut	–	Hazelnut, apple, peach, soybean, peanut, celery	0	3	3
12	43	F	–	–	–	n.a.	n.a.	0
13	58	F	Egg	–	–	1	0	0
14	40	M	–	–	–	n.a.	n.a.	0
15	29	M	–	–	–	n.a.	n.a.	0
16	53	M	–	–	–	n.a.	n.a.	0
17	26	F	–	–	–	n.a.	n.a.	0
18	60	M	–	Soybean	–	n.a.	n.a.	1
19	19	M	–	–	Apple	n.a.	n.a.	1
20	29	F	Fruit, nuts, peanut	–	–	3	0	0
21	29	M	Apple, pear, walnut	–	Hazelnut, apple, peanut	2	1	2
22	34	M	–	Walnut, kiwifruit	Hazelnut, apple, peach, peanut	n.a.	n.a.	6
23	47	F	–	–	–	n.a.	n.a.	0
24	62	F	–	–	–	n.a.	n.a.	0
25	42	F	Almond, apple, carrot, hazelnut, kiwifruit, peach, pear	Walnut	Hazelnut, apple, peach	4	3	1
26	21	M	–	Kiwifruit	Hazelnut, apple, peach, soybean, peanut	n.a.	n.a.	6
27	39	M	Banana, cod/crab/fish, kiwifruit	Cod, peanut, hazelnut, walnut, peach, shrimp	Hazelnut, apple, peach, soybean, peanut, celery	2	1	9

Table 3 (Continued)

Patient ID	Age, years	Sex	Self-reported food allergens	Sensitization pattern (CRD)		Patient query vs CRD		
				Primary food allergens, often causing systemic reaction	Cross-reactive food allergens	Self-reported allergens confirmed by CRD, N	Self-reported food allergens confirmed by CRD, N	Additional food allergen sensitizations by CRD, N
28	42	M	Almond, banana, cashewnut, hazelnut, kiwifruit, cow's milk, melon, wheat	Buckwheat, kiwifruit	Hazelnut	5	3	0
29	43	F	—	—	—	n.a.	n.a.	0
30	21	M	Egg, kiwifruit	Egg white	—	1	1	0
31	42	M	Apple, avocado, banana, kiwifruit, peach, pork, whey, pickles	—	—	8	0	0
32	34	F	Almond, celery, cucumber, fruit, hazelnut, paprika, tomato, walnut	—	Hazelnut, apple, peach, peanut, celery	5	4	1
33	21	M	Nuts, peanut, peas	Peanut	—	2	1	0
34	36	M	Apple, kiwifruit, nectarine, pear, walnut	—	Hazelnut, apple, peach, peanut	4	1	3
35	54	F	Fish, cow's milk	—	—	2	0	0
36	41	M	—	—	—	n.a.	n.a.	0
37	65	M	—	—	—	n.a.	n.a.	0
38	29	F	Apple	—	Hazelnut, apple, peach, soybean	0	1	3
39	27	F	—	—	—	n.a.	n.a.	0
40	46	M	—	—	—	n.a.	n.a.	0
41	49	M	Almond, apple, guacamole, papaya	—	Hazelnut, apple, peach	3	1	2
42	44	M	—	—	—	n.a.	n.a.	0
43	36	M	Hazelnut	—	Hazelnut	0	1	0
44	26	M	—	—	—	n.a.	n.a.	0
45	57	M	—	—	—	n.a.	n.a.	0
46	50	M	—	—	Hazelnut, peach	n.a.	n.a.	2
47	32	M	Apple, cheese	Kiwifruit	—	2	0	1
48	29	F	Pine nuts, rocket	—	—	2	0	0
49	46	M	Nuts, high yeast beer	—	Hazelnut	1	1	0
50	43	M	Kiwifruit, strawberry	Walnut	—	2	0	1

Table 3 (Continued)

Patient ID	Age, years	Sex	Self-reported food allergens	Sensitization pattern (CRD)		Patient query vs CRD		
				Primary food allergens, often causing systemic reaction	Cross-reactive food allergens	Self-reported food allergens not confirmed by CRD, <i>N</i>	Self-reported food allergens confirmed by CRD, <i>N</i>	Additional food allergen sensitizations by CRD, <i>N</i>
51	34	M	–	Walnut	Hazelnut, apple, peach, peanut	n.a.	n.a.	5
52	45	M	–	–	–	n.a.	n.a.	0
53	32	M	Melon, fish, walnut	–	Hazelnut, peach	3	0	2
54	41	M	–	–	–	n.a.	n.a.	0
55	49	M	Eggplant, hazelnut	–	Hazelnut, apple	1	1	1
56	31	M	Kiwifruit, sesame seed, tomato	–	–	3	0	0
57	18	F	–	–	–	n.a.	n.a.	0
58	45	M	–	–	–	n.a.	n.a.	0
59	25	M	Cow's milk	Cow's milk	–	0	1	0
60	46	M	–	–	–	n.a.	n.a.	0
61	39	M	–	–	Hazelnut, apple, peach, soybean, peanut	n.a.	n.a.	5
62	28	M	Kiwifruit, tuna	Peach	Hazelnut, apple, peach, soybean, peanut	2	0	5
63	66	M	–	–	–	n.a.	n.a.	0
64	26	M	Nuts	Walnut	Hazelnut, apple, peanut	0	1	3
65	35	M	–	–	Hazelnut, apple	n.a.	n.a.	2
66	48	M	–	–	–	n.a.	n.a.	0
67	31	M	–	–	–	n.a.	n.a.	0
68	20	M	Kiwifruit, hazelnut, peanut, soybean	Peanut	Hazelnut, apple, peach, soybean, peanut	1	3	2
69	53	M	Shellfish	–	–	1	0	0
70	29	M	Chickpeas, soybean, fish	–	–	3	0	0
71	24	M	Cow's milk	Cow's milk	Hazelnut, apple, peach, soybean, peanut	0	1	5
72	41	M	Cow's milk	–	–	0	0	0
73	20	M	Banana, walnut, spinach, broccoli, cauliflower, beans, leek	–	Soybean	7	0	1
74	26	M	Mushroom	–	Hazelnut, apple	1	0	2
75	38	M	–	–	–	n.a.	n.a.	0
76	38	M	–	–	–	n.a.	n.a.	0
Total, <i>N</i>			118	25	103	81	36	88

n.a., not applicable.

study is that we have not systematically compared CRD to SPT/APT or serum IgE CAP testing. However, a good correlation between CRD and serum IgE CAP testing has been demonstrated for aeroallergens in polysensitized patients (11).

This study may have clinical implications, which is currently being studied. As the results of conventional test-directed dietary therapy have been disappointing in adult EoE patients, the six food elimination diet (SFED) is currently most often advocated. SFED requires a very broad exclusion and reintroduction of foods, multiple endoscopies, and adherent patients (6, 7). As CRD enables testing for 112 allergen components, its yield may be higher than SPT. The characteristics of CRD could make it an interesting tool to direct individualized diets.

In conclusion, most adult EoE patients are polysensitized to food and aeroallergens. Food sensitizations in EoE are mainly caused by cross-reactivity to food allergens after primary birch pollen sensitization. Pollen and food sensitizations may cause or maintain esophageal inflammation in EoE patients. CRD provides more insight into the sensitization patterns, identifies additional food allergen sensitizations and might be useful to direct dietary therapy in EoE.

Author contributions

BvR contributed to conception and design of the study, acquisition, analysis and interpretation of data, drafting the article, and final approval of the version to be published. RvR contributed to conception and design of the study,

interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published. SV participated in analysis of data, drafting the article, and final approval of the version to be published. BVB participated in conception and design of the study, interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published. ABS contributed to conception and design of the study, interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published. IT contributed to conception and design of the study, interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published. AJS participated in conception and design of the study, revising the article critically for important intellectual content, and final approval of the version to be published. AB participated in conception and design of the study, acquisition and interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published.

Conflicts of interest

BvR, RvR, SV, BVB, ABS, IT, and AJS have no conflicts of interest pertinent to this paper. AB is supported by the Netherlands Organisation for Scientific Research (NWO), received research funding from AstraZeneca, Endostim, MMS, and Shire, and received speaker fees from MMS and Shire.

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