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BRIEF COMMUNICATION

Frequent sensitization to *Candida albicans* and profilins in adult eosinophilic esophagitis

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Candida albicans; eosinophilic esophagitis; food allergy; immunoglobulin E; profilin.

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Abstract

Background: Eosinophilic esophagitis (EoE) is often associated with atopic airway and skin diseases. More than 80% of EoE patients are sensitized to aero- and/or food allergens. Immunoglobulin (Ig)E-mediated immune responses to microbes have been reported to be deleterious in connection with atopic diseases.

Aim: The aim of this study was to obtain a comprehensive overview about the sensitization spectrum of adult EoE patients.

Methods: IgE in sera of 35 patients with active EoE were analyzed for reactivity to *Candida albicans,* as well as to a panel of recombinant and purified natural allergen components, using a microarray.

Results: IgE sensitization to Candida albicans was found in 43% of EoE patients. More than 80% of EoE patients were sensitized to aeroallergens and 22% to food-specific allergen components, whereas 69% of the patients exhibited specific IgE to cross-reactive allergens. Among the latter, profilins were identified as most frequent IgE cross-reactive allergen components. Interestingly, dysphagia, the main symptom of adult EoE patients following rice and/or bread ingestion, was associated with sensitization to cross-reactive allergens such as profilins, pathogenesis-related (PR) 10 and lipid transfer proteins (LTP). Intolerance toward meat rarely correlated with sensitization to animal food allergens.

Conclusion: Candida albicans and cross-reactive plant allergen components, in particular profilins, were identified as frequent sensitizers in adult EoE patients. Specific elimination therapies are suggested to reveal their actual roles in the pathogenesis of EoE.

Eosinophilic esophagitis (EoE) is a chronic inflammatory disease with characteristic intense infiltration of eosinophils into the esophageal epithelium resulting in esophageal dysfunction (1). EoE has been recognized as T-helper 2-type immune reaction (2). Its association with allergic diseases of the airways and/or skin has been observed in 68%, and 80% of all adult EoE patients are sensitized to aeroallergens and foods (3). Among pediatric EoE patients, 53% have been reported to respond to an elimination diet of food allergens identified by skin tests (4).

IgE-mediated immune reactions to microbes including *Candida albicans* have been associated with atopic diseases (5). As EoE patients might potentially suffer from a Candida infection owing to topical corticosteroid therapy, we investigated whether they develop a specific IgE sensitization.

Microarrays that allow testing of specific immunoglobulin (Ig)E antibodies to a panel of recombinant and purified natural allergen components have been shown to improve diagnostic and treatment decisions in allergic patients (6). The aim of our study was to comprehensively characterize the allergen sensitization profile of patients with EoE and to evaluate the biochip technology as a diagnostic tool for this disease. By correlating microarray results with clinical parameters, we aimed to get further information on the relevance of food allergen sensitization in order to plan rational allergen elimination strategies.

Methods

Thirty-five patients (30 men, mean age 37 ± 13; range 17–65 years) with active EoE, presenting with typical clinical signs and symptoms, endoscopic and histological findings, were included. All patients gave written informed consent before entering the study. The study was approved by the Ethics Committee of Canton Solothurn. A detailed patient history was obtained and peripheral blood was taken. Specific IgE levels for *C. albicans* were measured using ImmunoCAP (Thermo Fisher Scientific, Uppsala, Sweden). In addition, specific IgE antibodies against a panel of 112 aero- and food allergens were determined using ImmunoCAP-ISAC (Thermo Fisher Scientific).

Results

Candida sensitization is frequent

As EoE and atopic dermatitis (AD) share clinical and pathogenic features and sensitization to *C. albicans* plays a pathogenic role in AD (7), we investigated whether patients with EoE develop specific IgE to *C. albicans*. All of these patients had received topical corticosteroids for EoE in the past and had responded well to this treatment. None of them had clinical signs of active Candida infection when entering the study. We detected specific IgE to *C. albicans* in eight patients (20%), mean level 1.36 ± 1.06 kU/l (range 0.43–3.21 kU/l) corresponding to CAP class 1 and 2 in four patients each. In another seven patients, low levels (between 0.1 and 0.35 kU/l) of specific IgE against *C. albicans* were measured. Altogether, 43% of the EoE patients demonstrated IgE specific for *C. albicans*.

Predominant sensitization to aeroallergens

In our cohort of adult EoE patients, 74% reported additional allergic airway diseases (63% allergic rhinitis, 49% bronchial asthma) and 9% suffered from AD. In 32 of 35 EoE patients (91%), the microarray analysis revealed IgE against at least one of 112 allergen components tested. Figure 1 provides the spectrum and specific IgE levels against allergen components showing high variability. Highest IgE levels were observed to grass pollen and house dust mite allergen components. Two patients were exclusively sensitized to hymenoptera venom. Sensitization to aeroallergens was observed in 29 patients (83%), of them one exhibiting exclusively IgE against house dust mites. 28 patients (80%) were sensitized to pollen. In eight patients (23%), IgE to food-specific allergen components were detected.

Profilin represents the most frequent cross-reactive plant allergen

As EoE had been associated with food allergy, we specifically paid attention to IgE against food components. In contrast to the low rate of sensitizations to food-specific allergen components, sensitization to cross-reactive allergen components was detected in 69% of EoE patients. In parallel with the high number of patients sensitized to pollens, sensitization to cross-reactive plant allergen components was observed in 66% (Fig. 1). Sensitizations to profilins were the most frequent and found in 40% of the patients, followed by pathogenesis-related (PR)10 proteins (birch pollen Bet v1 homologues; 37%), lipid transfer proteins (LTP; 11%), thaumatin-like proteins (TLP; 11%), cross-reactive carbohydrate determinants (CCD; 8%), and polcacine (3%). Sensitizations to cross-reactive animal proteins were seen in three patients. Of two patients sensitized to serumalbumins, one had IgE to the bovine serumalbumin Bos d6.

Reported food intolerance is associated with sensitization to cross-reactive plant allergens

Next, we evaluated whether suspected food triggers for EoE correlated with sensitization to food allergens (Table 1). In all patients, dysphagia was associated with solid food uptake. 86% of EoE patients reported symptoms after ingestion of meat. However, in only one patient was IgE to animal food protein components detectable. In contrast, of 24 patients (69%) reporting rice triggering for EoE, 17 had IgE to cross-reactive plant allergens, predominantly to profilins and PR10 proteins in 13 and 11 patients, respectively. Three patients were sensitized to LTPs. Bread was not well tolerated by 10 patients, of which eight were sensitized to profilins. Dysphagia associated with apple ingestion was reported by 12 patients, of whom five reacted to PR10 proteins including three to the apple antigen Mal d1.

Discussion

Here, we report that adult EoE patients frequently develop IgE sensitization to *C. albicans*. The incidence in adults exceeded that of pediatric EoE patients (43% *vs* 9%) probably due to a longer disease course and/or repeated exposure to corticosteroids (8). As swallowed corticosteroids are used for treatment, EoE patients are prone to increased Candida colonization and infection of the oral cavity and esophagus (9). Candida was shown to induce the production of IL-5 (10) and, thus, may further contribute to eosinophil accumulation and activation in EoE. AD patients sensitized to *C. albicans* were reported to respond to an antimycotic therapy resulting in clinical improvement and decrease in serum IgE (7). Therefore, it seems likely that EoE patients colonized with and/or sensitized to Candida would profit from antimycotic therapy.

By applying microarray analysis using recombinant and highly purified allergen components, we have obtained new information on the sensitization spectrum of adult EoE patients. IgE against food-specific allergen components were rare compared with cross-reactive ones. Only one patient reacted to milk, none to eggs. In contrast, in pediatric EoE patients, specific IgE to milk (36%) and eggs have been detected much more frequently (8), suggesting that the sensitization spectra are different and might change over time. According to recent studies, six food elimination diet and

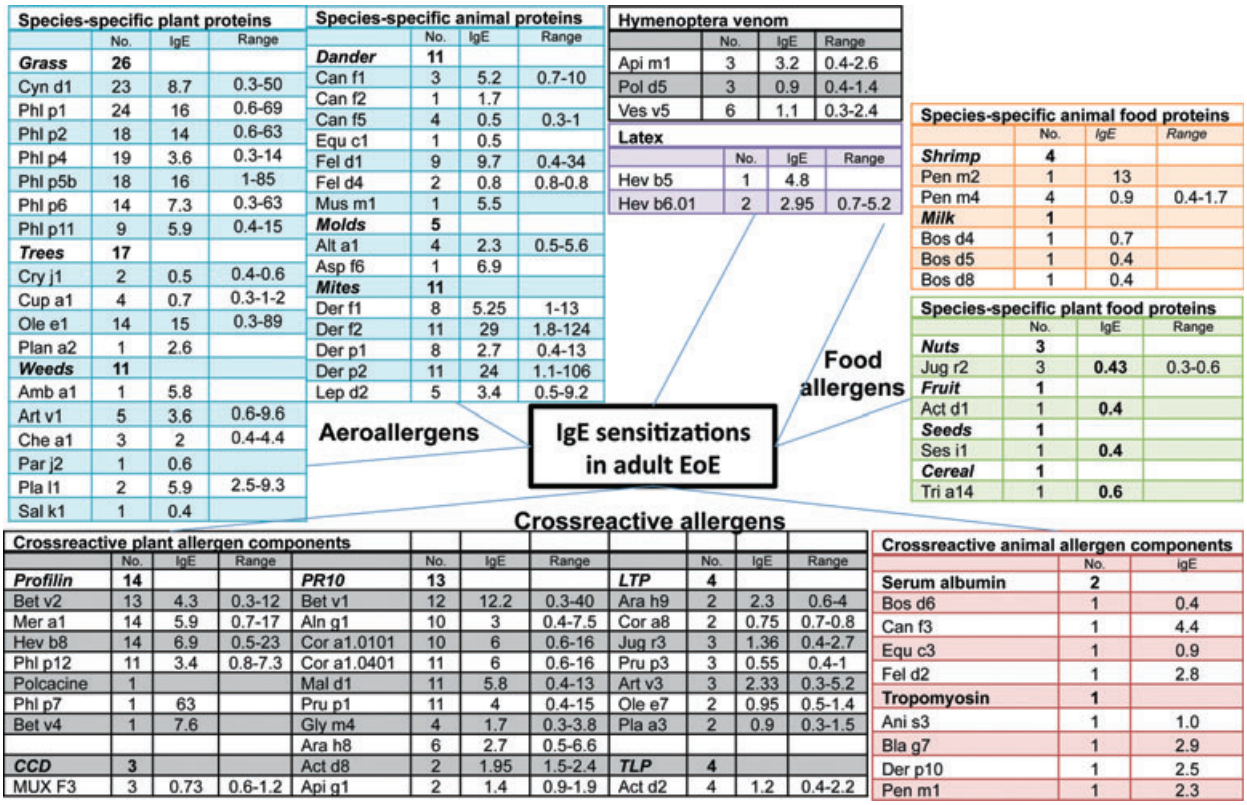

Figure 1 Sensitization spectrum of adult EoE patients. Number of sensitized patients and IgE levels (absolute value or mean and ranges in ISU) are given.

Table 1 The sensitization pattern to food allergens based on the reported trigger of dysphagia in adult EoE patients. The numbers patients with/without sensitization are given

			IgE to food allergens					
Reported trigger of dysphagia		No relevant IgE sensitization	Food-specific allergens		Cross-reactive food allergens			
Meat	30	29	1	Bos d 4, 5, 8	1	Bos d6		
Fish (tuna)	1	1	0		0			
Cheese	2	2	0		0			
			Cross-reactive plant allergens					
			PR10		*Profilin*		*LTP*	*TLP*
Rice	24	7	11		13	Phl p12 9	3	1
Apple	12	5	5	Mal d1 3	2		1	0
Bread	10	1	4		8	Phl p12 3	1	2
Vegetables	4	1	1		1		1	1
Marroni	1	1	0		0		0	0

subsequent food reintroduction might identify causative triggers of adult EoE independent of skin prick test results (11).

A correlation between dysphagia after meat ingestion with IgE sensitization to animal food allergens was not found, whereas dysphagia following uptake of plant-derived food was associated with sensitizations to cross-reactive plant allergens, suggesting their pathogenic role in EoE. Profilins were the most frequent cross-reactive allergens found. Sensitization to profilins was reported to be significantly associated with food allergy (12). Recently, wheat seed allergens, including profilin, have been identified to be responsible for food allergy (13). Wheat Tri a 36, a novel identified major food allergen, showed cross-reactivity with rice (14). Although rice

allergy is rare, anaphylactic reactions have been reported in LTP-sensitized patients (15). To prove the role of cross-reactive allergens, in particular profilins, as triggers of EoE, microarray evaluation of specific IgE against food allergen components, in addition to food provocation and/or elimination studies, will be required.

This study provided new insights in the sensitization profile of adult EoE patients. *C. albicans* and the cross-reactive plant components, in particular profilins, may represent potential candidates for therapeutic intervention in EoE.

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Conflict of interest

The authors declare no conflict of interest related to this manuscript.

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