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Food hypersensitivity reactions and peripheral blood eosinophilia in patients suffering from atopic dermatitis

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ABSTRACT

The aim of our study is to evaluate the count of eosinophils in peripheral blood in atopic dermatitis (AD) patients over 14 years of age and to compare it with the occurrence of food hypersensitivity (FH) reactions. Complete allergological and dermatological examination was performed in 212 patients included in the study (90 men, 122 women, average age 26.7 years, average SCORAD 32.9). According to our results, in AD patients the difference in count of eosinophils in patients with and without FH reactions is not statistically significant. When evaluating the occurrence of FH reactions to single foods, the count of eosinophils is significantly higher only in patients suffering from reactions to carrot.

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Introduction

Atopic dermatitis (AD) is a chronic noncontagious inflammatory skin disease with specific immune and inflammatory mechanisms; it is an inflammation of the epidermis and dermis with characteristic clinical and dermatopathological signs (Liu, Goodarzi, & Chen, 2011).

Food hypersensitivity (FH) reactions are a common finding in AD patients – in 78–83% (Celakovska & Bukac, 2015; Celakovska, Bukac, & Ettler, 2015). The term FH reaction represents the umbrella term for food allergy (IgE-, cellular-, and mixed IgE- and cell-mediated disorders) and for food intolerance (non-allergic FH) (Bindslev-Jensen et al., 2004; Li et al., 2001). Food intolerance is a non-allergic hypersensitivity to food that does not include the immune system even though the symptoms are similar to those of IgE-mediated allergic reactions. An impaired histamine degradation based on reduced diaminoxidase activity and the resulting histamine excess may cause numerous symptoms mimicking an allergic reaction (Maintz & Novak, 2007; Maintz et al., 2006). The ingestion of histamine-rich food or of alcohol or drugs that release histamine or block diaminoxidase activity may provoke diarrhea, headache, rhinoconjunctival symptoms, asthma, hypotension, arrhythmia, urticaria, pruritus, flushing, and other conditions in patients with histamine intolerance. Dermatologic sequels can be rashes, itch, urticaria,

angioedema, and AD. In addition to histamine-rich food, many foods such as citrus foods are considered to have the capacity to release histamine directly from tissue mast cells even if they themselves contain only small amounts of histamine (Maintz & Novak, 2007; Maintz et al., 2006). The occurrence of food intolerance, food allergy, and the occurrence of other atopic diseases and parameters in patients suffering from AD were evaluated in several studies (Breiteneder & Mills, 2005; Celakovska & Bukač, 2011; Celakovska, 2015; Celakovska & Bukač, 2015; Celakovska, Ettlerová, Vaněčková, & Ettler, 2011; Celakovska, Ettlerová, Ettler, Vaněčková, & Bukač, 2015a; Celakovska, Ettlerová, Ettler, Vaněčková, & Bukač, 2015; Celakovska, Ettlerová, Ettler, & Bukač, 2015).

Eosinophilia (more than 500 eosinophils per microliter of blood) has been shown to be present in most patients with AD and correlates with the disease activity (Celakovska et al., 2015b).

However, the diagnostic importance of eosinophilia has been unclear. Since increased blood eosinophils may exist due to any other allergic processes and some AD patients have normal blood eosinophil levels, blood eosinophil levels are not commonly used for diagnostic purposes (Kagi, Joller-Jemelka, & Wuthrich, 1992). More recent studies suggested that peripheral blood eosinophilia could be used as a diagnostic tool in differentiating atopic AD from non-atopic AD and that AD patients with other symptoms of atopy have increased blood eosinophilia. Recent studies in both adults and children have indicated a more prominent role of eosinophils in sensitized patients than in those not sensitized (Akdis et al., 1999; Borres & Bjorksten, 2004; Jenerowicz, Czarnecka-Operacz, & Silny, 2007; Noh et al., 2010; Park et al., 2006; Uehara, Izukura, & Sawai, 1990). There are also studies underlining the relation of eosinophil count, eosinophil-associated cytokines, and disease severity (Kondo, Yazawa, & Jimbow, 2001; Wu, Li, Chen, Cheng, & Wang, 2011). Regarding these results, it seems that eosinophils indicate both severity of disease and allergic sensitization. Eosinophils are also closely associated with the pathogenesis of other atopic diseases, specifically the development of allergic asthma in the respiratory tract and the development of eosinophilic esophagitis in gastrointestinal tract (Bochner & Busse, 2005; Cianferoni & Spergel, 2016).

But there are no studies evaluating the eosinophil count in AD patients with and without FH reactions.

The aim of our study is the evaluation of peripheral blood eosinophilia in AD patients with and without FH reactions.

Aim of the study

The aim is the evaluation of the correlation between the eosinophil count in the peripheral blood and the occurrence of FH reactions in AD patients.

Methods

In the period 2008–2013, 212 patients suffering from AD at the age of 14 years or older were included in the study. The diagnosis of AD was made with the Hanifin-Rajka criteria (Hanifin & Rajka, 1980). Exclusion criteria were long-term therapy with cyclosporin or systemic corticoids, pregnancy, or breastfeeding. Patients with AD having other systemic diseases were excluded from the study as well. Complete dermatological and allergological

examination was performed in patients included in the study. This study was approved by Ethics committee of Faculty Hospital Hradec Králové, Charles University of Prague, Czech Republic.

The count of eosinophils – it included differential white blood cell count with eosinophils. We used the standard microscopic cytology (with a manual review, May-Grünwald- and Giemsa – Romanowsky-type staining, microscop Olympus BX41 – product of Olympus, Hamburg, Germany) and flow cytometry (using Sysmex XE-5000, product of Sysmex, Kobe, Japan). About 5% of peripheral blood eosinophils and more was considered a higher count.

The diagnosis of FH reactions

All the patients were asked by the physician during the dermatological examination to complete the questionnaire concerning the food reactions. The answers concerning the possible adverse food reactions reflect the patients' history and are not based on the results of examinations (as specific IgE, skin prick tests [SPTs]). The patients were asked to describe only these reactions with clinical symptoms that had been repeatedly observed in their history and are reproducible after a casual ingestion. The most frequent food allergens were mentioned in the questionnaire (egg, cow milk, wheat flour, soy, celery, nuts, fish, different kinds of fruits and vegetables, spices, different kinds of meat, and alcohol) and patients answered if they had experienced some reactions to these foods such as pruritus, worsening of AD, erythema, urticaria, oral allergy syndrome (= burning of the mouth), gastrointestinal, or respiratory problems. Patients also described the time of these reactions (two hours after ingestion or later). The results of examinations, together with the patient's answers, were collected and processed by the dermatologist.

Statistics

We evaluated the difference in the count of eosinophils between AD patients with and without the occurrence of FH reactions. We also evaluated the difference in the count of eosinophils in AD patients suffering from FH reactions in general and in patients with FH reactions to single foods. Mann–Whitney test was used for comparison, because the underlying distributions are not normal (Gauss).

Results

Patients and tested parameters

About 212 patients suffering from AD at the age of 14 years or older were examined – 90 men and 122 women, the average age 27.1 years (s.d. 9.5 years), the average SCORAD 32.9 (s.d. 14.1) points. The average count of eosinophils in this group of patients is 5.4%; 166 patients (78%) suffer from FH reactions, in these patients the count of eosinophils is 5.8%; no FH reactions are in 46 patients (22%) and the count of eosinophils is in these patients 4%. The difference is not statistically significant.

The characteristics of 212 patients with AD and FH reactions are shown in [Table 1](#).

Table 1. Characteristics of patients.

No. of patients – 212 patients	
•	90 men and 122 women with the average age 27. 1 years (s.d. 9.5 years)
•	Average SCORAD – 32.9 (s.d. 14.1) points
•	Average eosinophils count – 5.5%
•	No. of patients with FH reactions – 166 (78%)
•	Average count of eosinophils – 5.8%
•	No. of patients without FH reactions – 46 (22%)
•	Average count of eosinophils – 4%

The occurrence of FH reactions with the clinical reactions and the count of eosinophils in these patients with FH reactions is shown in the Table 2. The FH reactions after the ingestion of nuts are described in 69 patients (32%), tomatoes in 41 patients (19%) kiwi in 35 patients (16%), apples in 35 patients (16%), spices in 42 patients (20%), tangerines in 30 patients (14%), oranges in 25 patients (12%), capsidum in 28 patients (13%) fish in 19 patients (9%), celery in 20 patients (9 %), and carrots in 14 patients (7%). In another 4–0.5% patients, the FH reactions were recorded after ingestion of these foods: strawberries, alcohol, chocolate, milk, almond, cherry, honey, potatoes, wine, apricots, garlic, poppy-seeds, cacao, pine-apple, banana, egg, gherkin, cucumbers, pears, pulses, beer, chees, beef, gooseberry, currants, melon, spinach, plum, rice, kohlrabi, ketchup, mustard, parsley, camomile, couliflower, chicken, ray flour, and maize. More than one kind of reactions were described in some patients (for example pruritus or oral allergy syndrome).

The number of patients with FH reactions to single foods and the count of eosinophils is recorded in Table 3. The difference in count of eosinophils is not statistically significant in patients with FH reactions to nuts, spices, tomatoes, kiwi, apple, tangerines, capsidum, oranges, fishes, celery, alcohol, strawberries, or chocolate in comparison to patients without these reactions. The difference is statistically significant only in patients suffering

Table 2. The occurrence of FH reactions, clinical reactions and the peripheral blood count of eosinophils in these patients with FH reactions.

No. of patients with food reactions		FH reactions				Count of eosinophils in %
		OAS	Pruritus	GI ^t symptoms	Worsening of AD	
Nuts	69 (32%)	61 (29%)	4 (2%)	6 (3%)	–	5.22
Spices	42 (20%)	32 (15%)	11 (5%)	–	–	4.95
Tomatoes	41 (19%)	31 (15%)	13 (6%)	–	–	5.69
Kiwi	35 (16%)	25 (12%)	15 (7%)	10 (5%)	–	6.54
Apple	35 (16%)	27 (13%)	4 (2%)	4 (2%)	–	4.52
Tangerines	30 (14%)	19 (9%)	13 (6%)	–	8 (4%)	8.39
Capsidum	28 (13%)	23(11%)	4 (2%)	4 (2%)	–	7.76
Oranges	25 (12%)	23 (11%)	10 (5%)	–	15 (7%)	8.86
Fish	19 (9%)	12 (6%)	15 (7%)	4 (2%)	–	4.97
Celery	20 (9%)	12 (6%)	15 (7%)	4 (2%)	–	7.32
Carrot	14 (7%)	4 (2%)	14 (7%)	–	–	9.17^a
Alcohol	10 (5%)	–	10 (5%)	–	–	4.40
Strawberry	9 (4%)	–	9 (4%)	–	–	5.14
Chocolate	7 (3%)	–	7 (3%)	–	–	3.02

Note: Number of patients from the total number of 212 (= 100%). The count of eosinophils more than 5% is recorded extra bold.

OAS, oral allergy syndrome; FH, food hypersensitivity reactions; GI^t, gastrointestinal symptoms; AD, worsening of atopic dermatitis.

^aThe difference is statistically significant.

Table 3. Number of patients with and without FH reactions to single foods and the peripheral blood count of eosinophils.

Tested parameter		Number of patients	Count of eosinophils in %
Nuts	FH+	69 (32%)	5.23
	FH–	143 (68%)	5.50
<i>p</i> value	.907710		
Spices	FH+	42 (20%)	4.95
	FH–	170 (80%)	5.52
<i>p</i> value	.931704		
Tomatoes	FH+	41 (19%)	5.69
	FH–	171 (81%)	5.34
<i>p</i> value	.3941		
Kiwi	FH+	35 (16%)	6.54
	FH–	177 (84%)	5.18
<i>p</i> value	.112574		
Apple	FH+	35 (16%)	4.525
	FH–	177 (84%)	5.587
<i>p</i> value	.851638		
Tangerines	FH+	30 (14%)	8.39
	FH–	182 (86%)	4.92
<i>p</i> value	.396276		
Capsidum	FH+	28 (13%)	7.76
	FH–	184 (87%)	5.05
<i>p</i> value	.402653		
Oranges	FH+	25 (12%)	8.86
	FH–	187 (78%)	4.95
<i>p</i> value	.1437		
Fishes	FH+	19 (9%)	4.97
	FH–	193 (91%)	5.45
<i>p</i> value	.429496		
Celery	FH+	20 (9%)	7.32
	FH–	192 (91%)	5.21
<i>p</i> value	.167787		
Carrot	FH+	14 (7%)	9.17
	FH–	198 (94%)	5.14
<i>p</i> value	.011409*		
Alcohol	FH+	10 (5%)	4.40
	FH–	202 (95%)	5.46
<i>p</i> value	0.1470		
Strawberries	FH+	9 (4%)	5.14
	FH–	203 (96%)	5.43
<i>p</i> value	.506820		
Chocolate	FH+	7 (3%)	3.02
	FH–	205 (97%)	5.49
<i>p</i> value	.281010		

Note: Number of patients from the total number of 212 (=100%).

*The difference is statistically significant.

to FH reactions to carrot: 14 patients (7%) suffer from reactions to carrot, in these patients the count of eosinophils is 9.2%; 198 patients (94%) suffer from no reactions to carrot and the count of eosinophils is in these patients 5.1% (Table 3).

Discussion

We performed this study to evaluate the count of eosinophils in peripheral blood in AD patients older 14 years of age and to compare this count of eosinophils according to the occurrence of FH reactions. There are no similar studies dealing with this question in AD patients.

In our study, we have not distinguished between food intolerance and food allergy, although the mechanisms leading to symptoms are very different, as mentioned in the introduction. Food intolerance reactions may cause numerous symptoms mimicking allergic reactions. The recorded early allergic reactions in our study have a high diagnostic importance because the early symptoms after ingestion of foods have a clear diagnostic connection with the ingested foods. The patients eliminate these foods but they describe that these reactions are reproducible after a casual ingestion. The aim of our study was to evaluate the occurrence of both types of food reactions in patients with AD and to compare the eosinophil count in AD patients with and without these reactions. Eosinophil numbers as well as eosinophil granule protein levels in the peripheral blood are elevated in most AD patients and appear to correlate with disease activity (Ring, Przybilla, & Ruzicka, 2006). These observations point to a potential important role of eosinophils in the pathogenesis of AD (Ring et al., 2006). Some patients exhibit normal blood eosinophil counts despite active AD and increased eosinophil numbers might be the consequence of additional allergic disorders. Recent studies in both adults and children have indicated the more prominent role of eosinophils in sensitized patients than in those not sensitized (Akdis et al., 1999; Borres & Bjorksten, 2004; Jenerowicz et al., 2007; Park et al., 2006; Uehara et al., 1990). Our paper shows that in AD patients suffering from FH reactions the blood eosinophilia is higher in comparison with patients without these reactions although the difference is not statistically significant. When evaluating the occurrence of FH reactions in general, the eosinophils count in patients with FH reaction is 5.8% (higher than normal count) and in patients without these reactions it is 4% (normal count), but the difference is not statistically significant. When evaluating the single foods, the most prominent eosinophilia is recorded in patients suffering to FH reactions to carrots; the count of eosinophils in these patients is 9.2%, and in the patients without reactions to carrot the eosinophil count is 5.1%; this difference is statistically significant. In patients with FH reactions to celery, tangerines, capsidum, oranges, and kiwi, the count of eosinophils is higher in comparison with patients without these reactions, but the difference is not statistically significant. On the other hand, in patients suffering from FH reactions to spices, apples, fishes, alcohol, and chocolate the count of eosinophils is under 5% and it is lower in comparison to patients without these reactions. Regarding the nuts and tomatoes, the eosinophils count is similar in patients with and without the reactions to these foods.

The statistically important difference was found only in patients with reactions to carrots. Regarding the described reactions to carrots in 14 patients (7%) in our study, all these patients suffer from pruritus after ingestion of carrot and oral allergy syndrome is recorded in four patients. In patients with FH reactions to carrot, the FH reaction to apple, capsidum, and nuts is recorded in the majority of them and 15 from 20 patients with FH reaction to carrots suffer from pollen allergy (Celakovska & Bukac, 2015; Celakovska et al., 2015).

According to Balmer-Webber, allergic reactions to carrot affect up to 25% of food-allergic subjects. In their study, double-blind placebo-controlled food challenges (DBPCFCs) were performed in 26 subjects with histories of allergic reactions to carrot. This study confirmed the allergenicity of carrot by means of DBPCFC. DBPCFC-positive patients had exclusively specific IgE antibodies to birch pollen-related carrot allergens, Dau c 1 being the major allergen. The lack of inhibition of IgE binding to Dau c 1 by birch allergens

in a subgroup of patients might indicate a secondary immune response to new epitopes on the food allergen that are not cross-reactive with Bet v 1 (Ballmer-Weber et al., 2001). Patients sensitized to birch pollen frequently suffer from a food allergy to plant foods such as celery, carrots, or hazelnut. One of the main manifestations of birch pollen-related food allergy is the oral allergy syndrome. Skin tests and specific IgE determinations are poor predictors of such reactions when assessed by DBPCFC (Ballmer-Weber, Weber, Vieths, & Wüthrich, 2008; Breiteneder & Mills, 2005; Skypala et al., 2011; Breiteneder & Radauer, 2004; Sánchez-Monge, Lombardero, García-Sellés, Barber, & Salcedo, 1999; Sinha et al., 2014).

Study evaluating the blood eosinophilia in AD patients was done in Japan (Kagi et al., 1992; Nishimoto, Numahara, Nakashima, & Yoshida, 1998). It was suggested that disease severity and personal or family history of respiratory atopy are important factors in determining high blood eosinophil levels in AD (Kagi et al., 1992). Akan evaluated the risk factors of disease severity to facilitate better management of children with severe AD (Akan et al., 2014). According to their results, eosinophilia may predict severe disease and allergic sensitization. Further large-scale follow-up studies are needed to improve the reliability and relevance of this relation (Akan et al., 2014). Accordingly, in a study in which both children and adults were enrolled, eosinophilia was found to be a predictor of food allergy in patients with AD. In this study, 303 patients with AD were studied using elimination diets and food challenge tests. An elimination diet improved clinical severity and decreased blood eosinophil levels (Celakovska, 2015). In the Jerenowicz's study, in patients with positive SPT test (grass pollen, tree pollen, weed pollen, feathers, and animal dander) and detectable specific IgE in serum, and also in patients with symptoms of other atopic diseases, the peripheral blood eosinophilia was more prominent compared to patients with negative SPTs and without symptoms of other atopic diseases, but the difference was not statistically significant (Akdis et al., 1999).

According to Ring, clinical improvements due to therapeutic interventions are associated with markedly reduced eosinophilic inflammation. Although these observations make it likely that eosinophil plays an important pathogenic role in AD, its exact function remains to be determined (Ring et al., 2006).

Conclusion

Our study evaluated the role of eosinophils in AD patients suffering from FH reactions. As for the single foods, the most prominent eosinophilia is recorded in patients suffering from FH reactions to carrot and the difference is statistically significant in comparison with patients without these reactions. In patients with FH reactions to celery, tangerines, capsicum, oranges, and kiwi, the count of eosinophils is higher in comparison with patients without these reactions, but the difference is not statistically significant.

Disclosure statement

No potential conflict of interest was reported by the authors.

Notes on Contributors

Jarmila Celakovska works as the specialist for atopic dermatitis in the Department of Dermatology and Venereology Faculty Hospital and Medical Faculty of Charles University, Hradec Králové, Czech Republic. At this Department, she works in the research of atopic dermatitis in the following of some immunological parameters such as food allergy and food sensitisation.

Josef Bukac is the mathematician, and works as a specialist for the statistical analysis at the Department of Medical Biophysics, Medical Faculty of Charles University in Hradec Králové, Czech republic.

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