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Atopic dermatitis in adolescents and adults – the evaluation of association with other allergic diseases and parameters

Jarmila Celakovska^a, Josef Bukač^b, Karel Ettler^c, Květuše Ettlerova^d and Irena Krcmova^e

^aDepartment of Dermatology and Venereology, Charles University, Hradec Králové, Czech Republic;

^bDepartment of Medical Biophysics, Charles University, Hradec Králové, Czech Republic; ^cDepartment of Dermatology and Venereology, University Hospital, Charles University, Hradec Králové, Czech Republic;

^dDepartment of Allergy and Clinical Immunology, Outpatient Clinic, Hradec Králové, Czech Republic;

^eDepartment of Clinical Immunology and Allergology, Faculty Hospital and Medical Faculty of Charles University, Hradec Králové, Czech Republic

ABSTRACT

There is a lack of reports focusing on the course of atopic dermatitis (AD) with respect to its evolution and association with other allergic diseases and parameters. This study gives the review of results concerning the evaluation of different parameters in patients suffering from AD older than 14 years of age. This study evaluates the occurrence of food allergy, food intolerance, inhalant allergy, occurrence of asthma bronchiale, allergic rhinitis, peripheral blood eosinophilia, family history of atopy, onset of AD and the severity of AD according to the SCORAD index.

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KEYWORDS

Food allergy; food intolerance; atopic dermatitis; asthma bronchiale; rhinitis; specific IgE

Introduction

There is a lack of reports focusing on the course of atopic dermatitis (AD) with respect to its evolution and association with other allergic diseases and parameters. AD is a chronic, intermittent, inflammatory, genetically predisposed skin disease characterized by severe pruritus, xerosis and maculopapulous rash. We give the review of our results concerning the evaluation of some parameters in patients suffering from AD older than 14 years of age; we summarize our results concerning the occurrence of food allergy, food sensitisation, food intolerance, inhalant allergy, occurrence of asthma bronchiale, allergic rhinitis, peripheral blood eosinophilia, family history of atopy, onset of AD and severity of AD in this group of patients. Many studies demonstrate the prevalence of allergic diseases; however, most studies analyzed a limited period from infancy to later childhood and/or to early adolescence. The progression of atopic disorders from AD in infants to allergic rhinitis and asthma in children is usually described as atopic march. Early childhood is thought to be a key period for the prevention of atopic march, and adolescence is another key period for the prevention of recurrence. Further prospective studies that use large cohorts are necessary to assess this issue (Kijima et al., 2013). Atopic march can occur at any age (Burgess et al., 2008); there is recent evidence that atopic march does not always follow the classic sequence (Barberio et al., 2008). Environmental and

genetic studies provide the evidence that a defect in epithelial barrier integrity may contribute to the onset of AD and progression of atopic march. Studies in animal models demonstrate that epidermal barrier dysfunction can be caused by repeated sensitization to allergens to the skin, which leads to phenotypes of AD and systemic sensitization and increased risk of allergic rhinitis, lung inflammation and airway hyperresponsiveness (He et al., 2009; Spergel et al., 1998).

Prevalence of AD in children varies worldwide from approximately 10–20% and AD may persist into adolescence or adult life in up to 10% of patients (Spergel, 2010; Zeppa, Bellini, & Lisi, 2011). Some hypotheses have been put forward to explain this trend, including diet, air pollution and the hygiene hypothesis. New insights into the genetics and pathophysiology of AD indicate the important role of structural abnormalities in the epidermis, as well as immune dysregulation (Boguniewicz & Leung, 2011; Howell et al., 2007; van den Oord & Sheikh, 2009; Weidinger et al., 2006). Defect of the skin barrier facilitates penetration and sensitization to food or airborne allergens, as well as infections by *Staphylococcus aureus*, herpes simplex virus or other microbes. Study of animals suggests that the environmental allergens, such as mites and food proteins, can make contact with the immune system via antigen-presenting cells in the superficial epidermis, leading to the sensitization, which could potentially make existing AD worse and may also be an important precursor of food and respiratory allergies (Barker et al., 2007; Bussmann, Böckenhoff, Henke, Werfel, & Novak, 2006; Fallon et al., 2009; Howell et al., 2007; Jeong et al., 2008; Kim, Leung, Boguniewicz, & Howell, 2008; Nemoto-Hasebe et al., 2009). Early epicutaneous sensitization to aeroallergens may be enhanced by damage of the skin barrier function, which is one of the major manifestations of AD and a key contributor to its pathogenesis. Abnormal expression of epidermal proteins caused by T_H2-type cytokines or protease allergens may increase the risk of sensitization to allergens and contribute to the development of AD (Boguniewicz & Leung, 2011; Fallon et al., 2009; Howell et al., 2007; Spergel, 2010; van den Oord & Sheikh, 2009; Weidinger et al., 2006; Zeppa et al., 2011). Airborne proteins have the ability to penetrate into the epidermis and worsen AD severity through the following three mechanisms: inherent proteolytic enzyme activity, activation of proteinase-activated receptors-2 (PAR-2) and immunoglobulin E (IgE) binding, leading to increased inflammation (Bussmann et al., 2006; Jeong et al., 2008). The theory describing atopic diseases as highly IgE dependent has persisted over a long time; however, a subgroup of atopic patients exhibits normal IgE levels and mechanisms contributing to the so-called “intrinsic” or “nonallergic form” have been the matter of intensive research work in the last years and new data have raised the question of the precise role of IgE in atopy. Some authors think that a strict distinction of intrinsic and extrinsic variant is impossible because intrinsic AD may develop into extrinsic over time (Roguedas-Contios & Misery, 2011). The hypothesis of a dynamic relationship between the two forms of AD is supported by the data in a study investigating the persistence of AD during the development of respiratory allergic diseases (Novembre et al., 2001). The level of total IgE is one of the main factors determining the variant of AD.

Food allergens have a well-known contribution to disease activity of AD, especially in infants and young children (Dai, 2007). Besides food allergy, food intolerance may contribute to the worsening of AD. The term food allergy is used to describe clinical symptoms, which are mediated by the immune system, and nonallergic food hypersensitivity to describe those which are not. The term food hypersensitivity represents the umbrella term for both

reaction patterns. For clinical implication, identification of individualized allergens is an ideal strategy for better control of AD and avoidance of atopic march (Dai, 2007). The higher prevalence of food allergy is recorded in children with atopic disorders; about 35% of children with moderate to severe AD have IgE-mediated food allergy and about 6–8% of asthmatic children have food-induced wheezing, but 80% of them outgrow their food allergy (Novembre, De Martino, & Vierucci, 1988). In adult patients with AD, studies investigating the co-prevalence of AD and food allergy are still scarce and exact data are not available (Heratizadeh, Wichmann, & Werfel, 2011; Werfel & Breuer, 2004; Worm et al., 2006).

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 (Liu, Goodarzi, & Chen, 2011). These observations point to a potential important role of eosinophils in the pathogenesis of AD (Liu et al., 2011).

Since some patients exhibit normal blood eosinophil counts despite active AD and since increased eosinophil numbers might be the consequence of additional allergic disorders, the determination of eosinophil number in blood is not a reliable tool in establishing the diagnosis of AD (Liu et al., 2011).

The severity of AD is usually evaluated with SCORAD index with assessment of topography items (affected skin area), intensity criteria and subjective parameters. The SCORAD index has been developed in consensus with the European Task Force on Atopic Dermatitis (ETFAD) in 1993. The acronym SCORAD was proposed by Arnold Oranje, and stands for SCORing AD (European Task Force on Atopic Dermatitis, 2004). By using this instrument, different studies are more comparable in routine practice, as well as in observational or double-blind randomized clinical trials (European Task Force on Atopic Dermatitis, 2004).

Aim of our study

- (1) To evaluate the relation between the severity of AD (SCORAD index) and the occurrence of food hypersensitivity reactions (food allergy, food intolerance), food sensitization and the occurrence of inhalant allergy.
- (2) To evaluate if the occurrence of food allergy and food sensitization in AD patients is in relation to other parameters, such as asthma bronchiale, allergic rhinitis, persistent eczematic lesions of AD, family history of atopy, occurrence of pollen allergy and onset of AD.
- (3) To evaluate if the occurrence of food hypersensitivity reactions (food intolerance, food allergy) is in relation to the occurrence of asthma bronchiale, allergic rhinitis, persistent eczematic lesions, family history of atopy and onset of AD.
- (4) To evaluate the relation between the level of total IgE (under/above 200 IU/ml) and the occurrence of some parameters in patients suffering from AD such as the occurrence of food allergy, the occurrence of food sensitization, pollen allergy, asthma bronchiale, allergic rhinitis, onset of AD, family history of atopy and persistent eczematic lesions.
- (5) To examine the sensitization to common inhalant allergens (dust, animal dander, bird feather and mites) in patients suffering from AD and to evaluate the relation between this sensitization and the occurrence of bronchial asthma, allergic rhinitis, persistent eczematic lesions, family history of atopy and the of AD.

- (6) To evaluate if the severity of AD (SCORAD index) is in relation to the occurrence of bronchial asthma, allergic rhinitis and occurrence of persistent eczematic lesions.
- (7) To evaluate the level of eosinophils in peripheral blood in AD patients and to compare it with the occurrence of food allergy and food intolerance in these patients. To evaluate if the level of eosinophils in peripheral blood is in relation to other parameters such as asthma bronchiale, allergic rhinitis, family history of atopy, persistent eczematic lesions, level of total IgE and onset of AD. To evaluate the relation between the level of eosinophils in peripheral blood and the severity of AD according to the SCORAD index.

Patients and methods

In the period 2005–15, we examined patients suffering from AD at the age of 14 years or older. The diagnosis of AD was made with the Hanifin–Rajka criteria (Hanifin & Rajka, 1980). We have created a unique group of patients, in which the different parameters concerning atopic march in 172–301 patients were studied. The detailed description of these studies is recorded in our previous publications (Celakovska, Bukac, & Ettler, 2015; Celakovska, Ettlerova, Ettler, & Bukač, 2015; Celakovska, Ettlerova, Ettler, Vaněčková, & Bukač, 2015; Celakovska & Bukac, 2015a, 2015b, 2016a, 2016b, 2017a, 2017b; Čelakovská, Krčmová, Bukač, & Vaněčková, 2017; Vaneckova & Bukac, 2016, 2017). All these patients were examined in the Department of Dermatology, Faculty Hospital Hradec Králové, Charles University of Prague, Czech Republic. Exclusion criteria were long-term therapy with cyklosporin or systemic corticoids, pregnancy, breastfeeding. Patients with AD having other systemic diseases were excluded from the studies as well. Complete dermatological and allergological examination was performed in patients included in the studies. These studies were approved by Ethics committee of Faculty Hospital Hradec Králové, Charles University of Prague, Czech Republic. After the discontinuation of antihistamines and topical steroids for at least 5 days and systemic steroids and UV therapy for at least 2 months, food allergy was examined (skin prick tests, specific IgE, atopy patch tests, diagnostic hypoallergenic diet, open exposure test, double-blind, placebo-controlled food challenge test).

A complete allergological examination was performed including the evaluation of the occurrence of asthma bronchiale, pollen allergy, rhinoconjunctivitis, skin prick test and specific IgE to inhalant and food allergens.

Regarding the evaluation of food hypersensitivity reactions, the patients answered if they had suffered from immediate or late food reactions (oral allergy syndrome, gastrointestinal problems, occurrence of skin problems, respiratory problems). The most frequent food allergens were mentioned and patients answered if they had suffered from some reactions to these foods; ideally they should have mentioned other foods with recorded reactions. The answers concerning the possible food hypersensitivity reactions reflect the patient's history and were not based on the results of examinations such as specific IgE, skin prick tests or challenge tests. The results of examinations with the patients' answers were collected and processed by the dermatologist.

The severity of AD was evaluated in our study with the SCORAD index with assessment of topography items (affected skin area), intensity criteria and subjective parameters.



Figure 1. Moderate form of atopic dermatitis with maculopapulous rash.

The intensity part of the SCORAD index consists of six items: erythema, edema/population, excoriations, lichenification, crusts and dryness. The subjective items included daily pruritus and sleeplessness. The severity of AD is evaluated with SCORAD as a mild form to 25 points, as moderate from 25 to 50 points and as severe form over 50 points (European Task Force on Atopic Dermatitis, 2004), (Figure 1 – moderate form of AD, Figure 2 – severe form of AD with severe lichenification).



Figure 2. Severe form of atopic dermatitis with lichenification.

The examination of blood eosinophils included differential white blood cell count with eosinophils. Standard microscopic cytology (with a manual review, May-Grünwald- and Giemsa – Romanowsky-type staining, microscope Olympus BX41 – product of Olympus, Hamburg, Germany) and flow cytometry were used (using Sysmex XE-5000, product of Sysmex, Kobe, Japan). 5% and more of peripheral blood eosinophils was evaluated as a higher count according to this laboratory method performed at the Haematology Department of Faculty Hospital Hradec Králové, Charles University of Prague, Czech Republic.

Results

We have created a unique group of patients, in which the different parameters concerning atopic march in 172–301 patients were studied (age 26.7–27.1 years, min.14 max. 63 years; with the median SCORAD 30.5 points, s.d. 12.4 max. 79.5 points, min. 12.5 points).

The mild form of AD was recorded in 31% patients, moderate form in 60% and severe form in 9% patients. The food allergy to egg white and yolk, peanuts, soy, cow’s milk and wheat was altogether confirmed in 28% patients; food sensitization to these foods was confirmed in 53%. The food hypersensitivity reactions were described in 78% of the patients. The sensitization to inhalant allergens was altogether confirmed in 70% patients – to mites in 60%, to feather in 13%, to animal dander in 44% and to dust in 22%. The occurrence of asthma bronchiale was recorded in 43% of patients, rhinitis in 74%, the persistent eczematous lesions in 62%, positive data about atopy in family history in 58%, onset of AD under 5 years of age in 77% and pollen allergy in 47% of patients. Total IgE under 200 IU/ml was recorded in 33% of patients and total IgE above 200 IU/ml was recorded in 67% of the patients. The count of eosinophils is normal (4.22%) in patients suffering from mild form of AD, but this count is higher in patients suffering from moderate and severe forms (5.68% and 6.73%). The survey of patients and of the tested parameters is shown in Tables 1–10.

Table 1. The relation between the severity of AD according to the SCORAD index (mild moderate, severe form of AD) and the occurrence of sensitization to mites, bird feather, animal dander, dust.

Sensitization to inhalant allergens	Number of patients from total number of patients 283 (=100%)		
	Mild form	Moderate form	Severe form
mites+	36 (40%)	115 (68%)	20 (80%)
mites–	53 (60%)	54 (32%)	5 (20%)
Total number of patients	89 (100%)	169 (100%)	25 (100%)
p-value		.0000^a	
bird feather +	9 (10%)	20 (12%)	9 (36%)
bird feather –	80 (90%)	149 (88%)	16 (64%)
Total number of patients	89 (100%)	169 (100%)	25 (100%)
p-value		.002^a	
animal dander+	28 (32%)	84 (50%)	14 (56%)
animal dander–	61 (68%)	85 (50%)	11 (44%)
Total number of patients	89 (100%)	169 (100%)	25 (100%)
p-value		.009^a	
dust+	7 (8%)	41 (24%)	14 (56%)
dust–	82 (92%)	128 (76%)	11 (44%)
Total number of patients	89 (100%)	169 (100%)	25 (100%)
p-value		.000^a	

Notes: Explanation: mites+: sensitization confirmed; mites–: sensitization not confirmed. Pairs of these categories were entered in contingency tables and the Chi-square test for independence of these variables was performed with the level of significance set to 5%.

^aThe correlation is shown in extra bold.

1. *The relation between the severity of AD and sensitization to inhalant allergy, food allergy, food sensitization and food hypersensitivity reactions.*

A significant relation was recorded between the severity of AD and sensitization to inhalant allergens. Patients suffering from moderate and severe forms of AD suffer significantly more often from sensitization to mites, animal dander, dust and feather in comparison to patients with mild form of AD (Celakovska & Bukac, 2017b), (Table 1 the rising occurrence of sensitization to inhalant allergens). A significant relation was also found between the severity of AD and the occurrence of early, combined and late IgE-mediated food allergy reaction. Food allergy was examined to cow milk, wheat, egg white and yolk, soy and peanuts. It turns out that the higher the time to food reaction the higher the severity of AD (Celakovska & Bukac, 2017b), (Table 2).

The occurrence of food sensitization to cow's milk, wheat, egg white and yolk, soy and peanuts is not in significant relation to the severity of AD (patients with positive results of sIgE and/or SPT and/or APT without the clinical symptoms) (Celakovska & Bukac, 2017b), (Table 2). Regarding the relation between the food hypersensitivity reactions and the severity of AD, we confirmed that patients with AD and food hypersensitivity reactions suffer significantly more often from moderate and severe forms of AD (Celakovska & Bukac, 2015b), (Table 2). The reactions to nuts, apples and fish are of great importance in relation to the severity of AD (Celakovska & Bukac, 2015b).

2. *The occurrence of food allergy and food sensitization and the relation to the occurrence of bronchial asthma, allergic rhinitis, family history of atopy, pollen allergy, onset of AD and persistent lesions of AD.*

In patients suffering from AD and food allergy to cow's milk, wheat, egg white and yolk, soy and peanuts, the occurrence of bronchial asthma, allergic rhinitis, family history of

Table 2. The relation between the severity of AD to the SCORAD index (mild, moderate, severe form of AD) and the occurrence of food allergy – early, combined, late reaction, food sensitization and occurrence of food hypersensitivity reactions.

FA	Number of patients from total number of patients 283 (=100%)			
	Mild form	Moderate form	Severe form	Total number of patients
FA+ early reaction	15 (5%)	14 (5%)	1 (0.3%)	30 (10%)
FA+ combined reaction	5 (2%)	27 (9%)	3 (1%)	35 (12%)
FA+ late reaction	4 (1.4%)	5 (1.7%)	4 (1.4%)	13 (4.5%)
FA–	65 (23%)	123 (44%)	17 (6%)	205 (72%)
Total number of patients	89 (31%)	169 (60%)	25 (9%)	283 (100%)
p-value			.005^a	
FS+	44 (15%)	91 (32%)	13 (4.5%)	148 (52%)
FS–	45 (16%)	78 (28%)	12 (4.5%)	135 (48%)
Total number of patients	89 (31%)	169 (60%)	25 (9%)	283 (100%)
p-value			.797	
FH+	Number of patients from total number of patients 285 (=100%)			
	Mild form	Moderate form	Severe form	Total number of patients
FH+	73 (81%)	125 (73%)	24 (96%)	222 (78%)
FH–	17 (19%)	45 (26%)	1 (4%)	63 (22%)
Total number of patients	90 (100%)	170 (100%)	25 (100%)	285 (100%)
p-value			.031^a	

Notes: FA: food allergy; FA+: food allergy confirmed; FA–: food allergy not confirmed; FS+: food sensitization confirmed; FS–: food sensitization not confirmed; FH+: positive data about food hypersensitivity reactions; FH–: no food hypersensitivity reactions.

Pairs of these categories were entered in contingency tables and the Chi-square test for independence of these variables was performed with the level of significance set to 5%.

^aThe correlation is shown in extra bold.

Table 3. Number of patients with confirmed food allergy (FA+) and without food allergy (FA–) and the occurrence of tested parameters.

Food allergy	Number of patients from total number of patients 272 (=100%)											
	AB+	AB–	RC+	RC–	Persistent	Occasional	History+	History–	AD Under 5 years	AD Later	Pollen allergy+	Pollen allergy–
FA+	47	31	71	7	62	16	59	19	63	15	56	22
	17%	11%	26%	3%	23%	6%	22%	7%	23%	5%	21%	8%
FA–	71	123	129	65	108	86	99	95	148	46	72	122
	26%	45%	47%	24%	40%	32%	36%	35%	54%	17%	26%	45%
Total	118	154	200	72	170	102	158	114	211	61	128	144
	43%	57%	74%	26%	62%	38%	58%	42%	77%	22%	47%	53%
p-value	.00037^a		.000^a		.000243^a		.000199^a		.442		.00000^a	

Notes: AB: asthma bronchiale; FA: food allergy; FA+: food allergy confirmed; FA–: food allergy not confirmed; RC+: rhinoconjunctivitis confirmed; RC–: rhinoconjunctivitis not confirmed. Pairs of these categories were entered in contingency tables and the Chi-square test for independence of these variables was performed with the level of significance set to 5%.

^aThe correlation is shown in extra bold.

Table 4. Number of patients with confirmed food sensitization and without food sensitization and the occurrence of tested parameters.

Food sensitization	Number of patients from total number of patients 272 (=100%)											
	AB+	AB–	RC+	RC–	Persistent	Occasional	History+	History–	AD Under 5 years	AD Later	Pollen allergy+	Pollen allergy–
Sensitization+	69	77	116	30	95	51	89	57	115	31	89	57
	25%	28%	43%	11%	56%	19%	33%	21%	42%	11%	33%	21%
Sensitization–	49	77	84	42	75	51	69	57	96	30	39	87
	18%	28%	31%	15%	28%	19%	25%	21%	35%	11%	14%	32%
Total	118	154	200	72	170	102	158	114	211	61	128	144
	43%	57%	74%	26%	62%	38%	58%	42%	77%	22%	47%	53%
p-value	.1647		.01715^a		.346		.301664		.611428		.00000^a	

Note: AB: asthma bronchiale, AB + asthma bronchiale confirmed, AB – asthma bronchiale not confirmed; RC+: rhinoconjunctivitis confirmed; RC–: rhinoconjunctivitis not confirmed; AD: atopic dermatitis.

^aThe correlation is shown in extra bold.

Table 5. The survey of examined patients with the occurrence of food hypersensitivity reactions and tested parameters.

FH	Number of patients from total number of patients 235 (=100%)						History		Onset of AD	Onset of AD
	AB+	AB–	RC+	RC–	Persistent	Occasional	+	–	under 5 years	above 5 years
FH+	88	108	155	41	127	69	112	84	151	45
	37%	47%	66%	18%	55%	29%	48%	36%	65%	19%
FH–	12	27	19	20	18	21	20	19	29	10
	5%	12%	9%	8%	8%	9%	9%	8%	13%	4%
Total number of patients	100	135	174	61	145	90	132	103	180	55
	42%	58%	74%	26%	62%	38%	56%	44%	77%	23%
p-value	.079		.0080^a		.03^a		.56		.837	

Notes: AB: asthma bronchiale; FH: food hypersensitivity reactions; FH+: positive data about food hypersensitivity reactions; FH–: no food hypersensitivity reactions. AB + asthma bronchiale confirmed, AB – asthma bronchiale not confirmed; RC+: rhinoconjunctivitis confirmed; RC – rhinoconjunctivitis not confirmed;

Pairs of these categories were entered in contingency tables and the Chi-square test for independence of these variables was performed with the level of significance set to 5%.

^aThe correlation is shown in extra bold.

Table 6. The relation between the level of total IgE (under/above 200 IU/ml) and the occurrence of followed parameters in patients suffering from AD.

Followed parameters	Number of patients from total number of patients 277(=100%)		
	Total IgE under 200 IU/ml	Total IgE above 200 IU/ml	Number of patients
asthma br.+	24 (9%)	96 (35%)	120 (43%)
asthma br.–	68 (24%)	89 (32%)	157 (57%)
Total number of patients	92 (33%)	185 (67%)	277 (100%)
p-value	.000^a		
rhinitis+	46 (17%)	156 (56%)	202 (73%)
rhinitis–	46 (17%)	29 (10%)	75 (27%)
Total number of patients	92 (33%)	185 (67%)	277 (100%)
p-value	.000^a		
history+	41 (15%)	121 (44%)	162 (59%)
history–	51 (18%)	64 (23%)	115 (41%)
Total number of patients	92 (33%)	185 (67%)	277 (100%)
p-value	.001^a		
food allergy+	12 (4%)	66 (24%)	78 (28%)
food allergy–	80 (29%)	119 (43%)	199 (72%)
Total number of patients	92 (33%)	185 (67%)	277 (100%)
p-value	.000^a		
food sensitization+	36 (13%)	110 (40%)	146 (53%)
food sensitization–	56 (20%)	75 (27%)	131 (47%)
Total number of patients	92 (33%)	185 (67%)	277 (100%)
p-value	.002^a		
pollen allergy+	25 (9%)	104 (37%)	129 (46%)
pollen allergy–	67 (24%)	81 (30%)	148 (54%)
Total number of patients	92 (33%)	185 (67%)	277 (100%)
p-value	.000^a		
Persistent lesions	33 (12%)	142 (51%)	175 (63%)
Occasional lesions	59 (21%)	43 (15%)	102 (36%)
Total number of patients	92 (33%)	185 (67%)	277 (100%)
p-value	.000^a		
AD under 5 years	58 (21%)	156 (56%)	214 (77%)
AD above 5 years	34 (12%)	29 (10%)	63 (22%)
Total number of patients	92 (33%)	185 (67%)	277 (100%)
p-value	.000^a		

Notes: Pairs of these categories were entered in contingency tables and the Chi-square test for independence of these variables was performed with the level of significance set to 5%.

^aThe correlation is shown in extra bold.

Table 7. The relation between the occurrence of sensitization to inhalant allergens in AD patients and the occurrence of followed parameters.

Tested parameters	Number of patients from total number of patients 288 (=100%)									
	AB+	AB–	RC+	RC–	Persistent lesions	Occasional lesions	Onset of AD under 5 years	Onset later	Family history+	Family history–
mites+	93	82	144	31	125	50	138	37	114	61
	32%	28%	50%	11%	44%	17%	48%	13%	40%	21%
mites–	32	81	67	46	53	60	82	31	50	63
	11%	28%	23%	16%	18%	21%	28%	11%	17%	22%
Total number of patients	125	163	211	77	178	110	220	68	164	124
	43%	57%	73%	27%	62%	38%	76%	24%	57%	43%
<i>p</i> -value	.000^a		.000^a		.000^a		.219		.0004^a	
feather+	16	22	31	7	24	14	23	15	21	17
	5%	8%	11%	2%	8%	5%	8%	5%	7%	6%
feather–	109	141	180	70	154	96	197	53	143	107
	38%	49%	62%	24%	53%	33%	68%	18%	50%	37%
Total number of patients	125	163	211	77	178	110	220	68	164	124
	43%	57%	73%	27%	62%	38%	76%	24%	57%	43%
<i>p</i> -value	.862		.2138		.8539		.0134^a		.8222	
dust+	32	31	55	8	50	13	49	14	46	17
	11%	11%	19%	3%	18%	5%	17%	5%	16%	6%
dust–	93	132	156	69	128	97	171	54	118	107
	32%	46%	54%	24%	44%	34%	60%	19%	41%	37%
Total number of patients	125	163	211	77	178	110	220	68	164	124
	43%	57%	73%	27%	62%	38%	76%	24%	57%	43%
<i>p</i> -value	.1805		.0043^a		.0011^a		.769		.0035^a	
animal dander+	77	51	109	19	92	36	112	16	88	40
	37%	17%	38%	7%	32%	12%	39%	6%	31%	14%
animal dander–	48	112	102	58	86	74	108	52	76	84
	17%	39%	36%	20%	30%	26%	38%	18%	26%	29%
Total number of patients	125	163	211	77	178	110	220	68	164	124
	43%	57%	73%	27%	62%	38%	76%	24%	57%	43%
<i>p</i> -value	.000^a		.000^a		.0016^a		.00000^a		.000296^a	

Notes: AB + asthma bronchiale confirmed, AB - asthma bronchiale not confirmed; RC+: rhinoconjunctivitis confirmed; RC: rhinoconjunctivitis not confirmed; mites+: sensitisation confirmed; mites–: sensitisation not confirmed.

Pairs of these categories were entered in contingency tables and the Chi-square test for independence of these variables was performed with the level of significance set to 5%.

^aThe correlation is shown in extra bold.

Table 8. The relation of the severity of atopic dermatitis (SCORAD index) to the occurrence of bronchial asthma, allergic rhinitis and occurrence of persistent eczematic lesions.

Followed parameters	Number of patients from total number of patients 283 (=100%)			
	Mild form	Moderate form	Severe form	Total number of patients
No. of patients AB+	31 (11%)	77 (27%)	16 (6%)	124 (44%)
No. of patients AB–	58 (20%)	92 (33%)	9 (3%)	159 (56%)
Total number of patients	89 (31%)	169 (60%)	25 (9%)	283 (100%)
<i>p</i> -value	.026^a			
No. of patients RC+	58 (20%)	128 (45%)	24 (8.7%)	210 (74%)
No. of patients RC–	31 (11%)	41 (15%)	1 (0.3%)	73 (26%)
Total number of patients	89 (31%)	169 (60%)	25 (9%)	283 (100%)
<i>p</i> -value	.006^a			
No. of patients persistent I+	34 (12%)	117 (42%)	24 (8.7%)	175 (62%)
No. of patients persistent I–	55 (19%)	52 (18%)	1 (0.3%)	108 (38%)
Total number of patients	89 (31%)	169 (60%)	25 (9%)	283 (100%)
<i>p</i> -value	.000^a			

Notes: AB: asthma bronchiale; RC: rhinoconjunctivitis. AB + asthma bronchiale confirmed, AB - asthma bronchiale not confirmed ; RC+: rhinoconjunctivitis confirmed; RC : rhinoconjunctivitis not confirmed; persistent I+: positive occurrence of persistent lesions, persistent I–: no persistent lesions.

Pairs of these categories were entered in contingency tables and the Chi-square test for independence of these variables was performed with the level of significance set to 5%.

^aThe correlation is shown in extra bold.

Table 9. The occurrence of food hypersensitivity reactions with the symptoms and the peripheral blood count of eosinophils in these patients with FH reactions.

No. of patients with FH reactions		FH reactions in 212 (= 100 %) patients included in the study				Count of Eosinophils in %
		OAS	pruritus	GIT symp	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

Notes: OAS: oral allergy syndrome; FH: food hypersensitivity reactions; GIT: gastrointestinal symptoms AD-worsening of atopic dermatitis

Number of patients from the total number of 212 (=100%). The count of eosinophils more than 5% is recorded in extra bold. Mann–Whitney Test for Difference in Medians was used for statistical evaluation.

^aThe correlation is shown in extra bold.

Table 10. The peripheral blood count of eosinophils and the relation to the occurrence of asthma bronchiale, rhinoconjunctivitis, food allergy, food sensitization, the level of total IgE, onset of AD, family history, duration of the eczematic lesions, the severity of AD.

Followed parameters	Number of patients from total number of patients 172 and the count of eosinophils in %			
AB	AB+ 76 p.	6.28%	AB– 96 p.	4.71%
RC	RC+ 129 p.	5.81%	RC– 43 p.	4.16%
FA	FA+ 55 p.	6.10%	FA– 117 p.	5.12%
FS	FS+ 96 p.	4.96%	FS– 76 p.	5.96%
Total IgE	Positive 121 p.	6.01%*	Negative 51 p.	3.68%*
Onset of AD	Under 5 years 133 p.	5.88%	Above 5 years 39 p.	3.62%
Family history	Positive 101 p.	5.78%	Negative 71 p.	4.78%
Duration of lesions	Permanent 122 p.	6.03%	Occasional 60 p.	4.22%
Mild AD	49 p.	4.22%		
Moderate AD	107 p.	5.68%		
Severe AD	16 p.	6.73%		

Notes: AB + asthma bronchiale confirmed, AB - asthma bronchiale not confirmed ; RC+: rhinoconjunctivitis confirmed; RC : rhinoconjunctivitis not confirmed; p: patients, FA+: positive finding of food allergy; FA–: negative finding of food allergy; FS+: food sensitization confirmed; FS–: food sensitization not confirmed.

Total IgE: positive – above 200 IU/ml, negative – under 200 IU/ml.* indicates the difference is statistically significant. mild AD, moderate AD, severe AD – according to the SCORAD index. Number of patients from the total number of 172. Mann–Whitney Test for Difference in Medians was used for statistical evaluation. The correlation is shown in extra bold.

atopy, pollen allergy and persistent lesions of AD are recorded significantly more often in comparison to patients without food allergy to these food allergens (Celakovska & Bukac, 2015a), (Table 3) . In patients with food sensitization to cow’s milk, wheat, egg white and yolk, soy and peanuts the occurrence of pollen allergy and allergic rhinitis is significantly higher than in patients without food sensitization. The food allergy to wheat, soy and peanuts is important (Table 4) (Celakovska & Bukac, 2015a).

3. *The occurrence of food hypersensitivity reactions and the relation to the occurrence of bronchial asthma, allergic rhinitis, family history of atopy, onset of AD and persistent lesions of AD.*

Atopic march was confirmed in patients suffering from AD and from food hypersensitivity reactions (Celakovska, Bukac, & Ettler, 2015), (Table 5). The moderate and severe forms of AD are recorded significantly more often in patients suffering from food hypersensitivity reactions as mentioned above (Table 2); these patients suffer as well significantly more often from allergic rhinitis and persistent eczematic lesions. Patients with reactions to nuts suffer more often from bronchial asthma and allergic rhinitis; the reaction to kiwi and fish is recorded more often in patients with persistent eczematic lesions, and reaction to apples is recorded more often in patients with allergic rhinitis (Celakovska, Bukac, & Ettler, 2015).

4. *The level of total IgE (under/above 200 IU/ml) and the relation to the occurrence of bronchial asthma, allergic rhinitis, family history of atopy, onset of AD, food allergy, food sensitization, pollen allergy and persistent lesions of AD.*

The level of total IgE is the important parameter for the evaluation of other signs of atopy in patients suffering from AD. In these patients with the level of total IgE above 200 IU/ml, the occurrence of bronchial asthma, allergic rhinitis, positive family history of atopy, food allergy and food sensitization, persistent eczematic lesions and the onset of AD under 5 years of age are recorded significantly more often than in patients with the level of total IgE under 200 IU/ml (Table 6), (Celakovska, Ettlerova, Ettler, & Bukač, 2015).

5. *The sensitization to inhalant allergens and the relation to the occurrence of bronchial asthma, allergic rhinitis, family history of atopy, onset of AD and persistent lesions of AD.*

AD, asthma bronchiale and rhinitis have their own association with aeroallergens. Asthma bronchiale is recorded significantly more often in AD patients suffering from sensitization to animal dander and mites; rhinitis in patients suffering from sensitization to animal dander, mites and dust. Persistent lesions of AD occur more often in patients with sensitization to animal dander, mites and dust. The onset of AD above 5 years of age is recorded significantly more often in patients with sensitization to bird feather; in these patients, there is no relation to the occurrence of family history of atopy. On the other hand, the onset of AD under 5 years of age is recorded more often in patients sensitized to animal dander (Table 7), (Celakovska, Ettlerova, Ettler, Vaněčková, et al., 2015).

6. *The severity of atopic dermatitis (SCORAD index) and the relation to the occurrence of bronchial asthma, allergic rhinitis and occurrence of persistent eczematic lesions.*

A significant relation was recorded between the severity of AD (evaluated with the SCORAD index) and the occurrence of bronchial asthma, allergic rhinitis and the persistent eczematic lesions. The occurrence of bronchial asthma, allergic rhinitis and persistent eczematic lesions was significantly higher in moderate and severe forms of AD (Table 8), (Celakovska & Bukac, 2016b).

7. *The peripheral blood count of eosinophils and the relation to the occurrence of asthma bronchiale, rhinoconjunctivitis, food allergy, food sensitization, the level of total IgE, onset of AD, family history, duration of the eczematic lesions, the severity of AD and the occurrence of food hypersensitivity reactions.*

Our results confirm that blood eosinophilia could be used as a diagnostic tool in differentiating extrinsic, allergic AD from intrinsic, nonallergic variant of AD. In AD patients with asthma bronchiale, rhinitis, food allergy, positive family history of atopy, with permanent skin lesions, with total IgE above 200 IU/ml, with the onset of AD under 5 years of age and in patients suffering from moderate or severe form of AD, the count of eosinophils in peripheral blood is higher than the normal level of eosinophils (above 5%), (Table 9), (Celakovska & Bukac, 2016a). Regarding the role of eosinophils in AD patients suffering from food hypersensitivity reactions, the most prominent eosinophilia is recorded in patients suffering from food hypersensitivity reactions to carrot and the difference is statistically significant in comparison with patients without these reactions. In patients with food hypersensitivity reactions to celery, tangerines, capsicum, oranges and kiwi, the count of eosinophils is higher in comparison to patients without these reactions, but the difference is not statistically significant (Table 10), (Celakovska & Bukac, 2017a).

Conclusion

Atopic dermatitis (AD), asthma bronchiale and rhinitis have their own association with aeroallergens and food allergens. In patients suffering from AD and food allergy, the occurrence of bronchial asthma, allergic rhinitis, family history of atopy, pollen allergy and persistent lesions of AD is recorded significantly more often in comparison to patients without food allergy. A significant relation was also found between the severity of AD and the occurrence of early, combined and late IgE-mediated food allergy reaction. It turns out that the higher the time to food reaction the higher the severity of AD. Patients with AD and food hypersensitivity reactions suffer significantly more often from the moderate and severe forms of AD. The occurrence of bronchial asthma, allergic rhinitis and persistent eczematous lesions was significantly higher in moderate and severe forms of AD. Regarding the inhalant allergens, asthma bronchiale is recorded significantly more often in AD patients suffering from sensitization to animal dander and mites; rhinitis in patients suffering from sensitization to animal dander, mites and dust. Patients suffering from moderate and severe forms of AD suffer significantly more often from sensitization to mites, animal dander, dust and feather in comparison to patients with a mild form of AD. Our results confirm that blood eosinophilia could be used as a diagnostic tool in differentiating extrinsic, allergic AD from intrinsic, nonallergic variant of AD.

Disclosure statement

No potential conflict of interest was reported by the authors.

Notes on contributors

Jarmila Celakovska works as the specialist for atopic dermatitis at the Department of Dermatology and Venereology Faculty Hospital and Medical Faculty of Charles University, Hradec Králové, Czech Republic. She works in the research of atopic dermatitis in the following of some immunological parameters in patients suffering from atopic dermatitis especially she is interested in examination of food allergy in patients suffering from this disease.

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.

Karel Ettler works as the specialist at the Department of Dermatology and Venereology Faculty Hospital and Medical Faculty of Charles University, Hradec Králové, Czech Republic.

Květuše Ettlerova works in Department of Allergy, Outpatient Clinic, Hradec Králové, Czech republic.

Irena Krčmova works as the specialist for immunology and allergy at the Department of Clinical immunology and Allergology, Faculty Hospital and Medical Faculty of Charles University, Hradec Králové, Czech Republic.

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