Original paper

Disease extent and severity in patients with atopic dermatitis and food allergy

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Abstract

Introduction: Subjective incidence of symptoms of food allergy (FA) is very high among patients with atopic dermatitis (AD), yet standardized procedures rarely confirm IgE-dependent sensitization.

Aim: Investigation of the incidence of IgE-dependent FA and airborne allergy in AD patients. Clinical evaluation of AD patients considering the coexistence of IgE-related sensitization to environmental allergens.

Material and methods: Hundred and two patients with AD, controls: 20 patients with allergic rhinitis (AR), 20 healthy volunteers. In AD patients > 4 years skin prick tests (SPT) with airborne allergens; depending on age, SAFT, APT or SPT with food allergens. Evaluation of disease extent and severity with two scores: SCORAD and W-AZS.

Results: Symptoms of FA were reported by 68%, while IgE-dependent FA was diagnosed exclusively in children < 5 years (16% of the population); airborne allergy in 63% of the examined population. Extrinsic phenotype of AD (eAD) was observed in 71%, intrinsic (iAD) in 29%. Increased W-AZS was observed in AD patients with FA compared with the rest of the AD population ($p = 0.006$), eAD with airborne allergy ($p = 0.041$) and iAD ($p = 0$). Increased SCORAD was observed in AD patients with FA compared to the rest of the AD group ($p = 0.005$) and iAD ($p = 0$).

Conclusions: A significant difference was observed in the incidence of self-reported symptoms of FA between the AD group and IgE-dependent FA, while airborne allergy was observed in the majority of patients. Statistically higher scores of W-AZS and SCORAD index indicate that food allergens may play some role in the development of AD in children.

Key words: atopic dermatitis, food allergy, skin application food test, atopy patch test, skin prick tests.

Introduction

Over the past 30 years, an increase in the incidence of allergic diseases, such as food allergy (FA), allergic contact dermatitis (ACD), atopic dermatitis (AD), allergic rhinitis (AR) and asthma, has been observed [1-4]. Nowadays, it is estimated that up to 30% of the population of developed countries suffers from allergic diseases [1, 2]. Moreover, a triple-fold increase of the incidence of atopic dermatitis was observed, which affects 2-10% of adults and 15-30% of children among the European population [3, 5-7]. According to the World Helath Organization, FA affects 6-8% of neonates, 3-5% of children and 2-4% of adults. It is estimated that IgE-dependent FA may affect up to 25-50% of children with AD, which is characterized by elevated levels of antigen-specific IgE (asIgE) [8-10].

It is considered that in children with AD, food allergens may play a noticeable role in the development of inflammation in the skin. The FA appears usually as the first allergic disease during a lifetime. The FA is usually a result of structural, functional and immunological immaturity of the gastrointestinal system, exposed to the unusually potent allergens of cow's milk proteins (CMP) [10-14]. The immune barrier of the gastrointestinal system in most neonates and children becomes impenetrable with time, which leads to the development of tolerance towards sensitizing proteins [15-20]. However, the development of airborne sensitization is observed in most AD patients with a history of FA, by the age of 5-8 years, in the form of allergic rhinitis and/or allergic conjunctivitis or asthma [12, 15, 16]. The FA used to be considered as a significant factor related to the onset of AD in neonates. Nowadays many authors suggest a more cautious approach regarding this issue [13, 21, 22]. The pathogenesis of AD is more complex, and FA is only one among many external factors influencing the course of AD. Moreover, it is often difficult to prove the relationship between

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exposure to sensitizing foods and exacerbation of AD [11-14, 20]. On the other hand, airborne allergy seems to be one of the most important external factors influencing the development and the course of AD, as IgE-dependent sensitization to inhalant allergens, since it is observed in up to 80% of patients [15-18, 23]. Patients with AD often report aggravation of the disease after exposure to airborne allergens, having no symptoms from the respiratory system at the same time. The most important airborne allergens in patients with AD are house dust mites (HDM), pollen related allergens and animal dander [1, 6, 11]. Some airborne allergens are also related to oral allergy syndrome (OAS), related to cross-reactivity to food allergens. Due to the presence of very similar antigen determinants and thus IgE antibodies, patients allergic to airborne allergens may present signs of food intolerance after the consumption of numerous foods. For example, birch and mugwort pollen-allergic individuals may experience an itching sensation or angioedema/urticaria after consuming fresh fruits (apple, peach) and vegetables (carrot, celery, potato). Moreover, animal dander allergy may induce reactions after consumption of pork, while HDM sensitized patients will not tolerate crustaceans. In up to 80% of adults with the suspicion of FA, cross-reactions to food allergens in the course of airborne allergy are the main cause of symptoms of food intolerance [17, 23, 24-26].

Aim

The main objective of this study was to investigate the incidence of subjective symptoms of FA and IgE-dependent FA, as well as airborne allergy in the population of patients with AD, estimated on the basis of conventional diagnostic procedures. Furthermore, the secondary aim was to estimate and compare clinical evaluation of skin inflammation extent and severity in AD patients considering the coexistence of IgE-related sensitization to environmental allergens, using two independent systems: SCORAD and W-AZS.

Material and methods

We studied a total of 102 patients with AD and 40 patients in two control groups: 20 patients with AR and 20 healthy individuals. The mean age in the group of AD patients was 9.7 ±9.1 years (1-30 years), and the group consisted of 57.8% female, and 42.2% male individuals. In the investigated AD group 75.5% were children (below 18 years of age) and 24.5% were adults.

The first control group consisted of 20 patients with AR, 10 female and 10 male individuals. The mean age in the AR group was 29.4 ±7.45 years (9-44 years).

The second control group consisted of 20 healthy individuals with no history of chronic diseases and no allergic symptoms. The mean age in the group was 27.7 ±3.7 years, and the group consisted of 7 male (35%) and 13 female (65%) patients.

After a thorough clinical examination by a dermatologist, the diagnosis of AD was established. In AD patients above 4 years of age skin prick tests (SPT) with both food and airborne allergens, while in AD patients below 4 years of age skin application food test (SAFT) and atopy patch test (APT) with native food allergens were performed. Additionally, in all children with AD aged below 9 years SAFT and APT were performed. In patients in the two control groups SPT with both food and airborne allergens were performed.

The SPT were performed in AD patients above 4 years of age using standardized extracts of both food (CMP, hen's egg, wheat, cocoa, peanut, apple, celery and carrot) and airborne allergens (grasses and grains, weeds, trees, moulds, animal dander and HDM; Nexter – Allergopharma, Germany). The SAFT and APT analyses in AD patients below 9 years of age were performed using native food allergens (cow's milk, egg white, egg yolk, wheat flour, cocoa, apple, carrot, celery and peanut). In children between 4 years and 9 years SAFT, APT and SPT with food allergens and SPT with airborne allergens were performed. In children with AD below 4 years of age SPT with airborne allergens were not performed, due to personal observations and available data on minor usefulness of SPT in this age group. Different response to histamine in children below 4 years of age, and the pain and stress related to the procedure may influence the final results of SPT in this age group.

Clinical evaluation of skin inflammation extent and severity in AD patients was performed using two independent systems: the commonly known SCORAD and W-AZS [27, 28]. In AD patients and in the two control groups total serum IgE (tIgE) was measured using the FEIA Cap System (Uppsala, Sweden). Additionally in AD patients antigen-specific IgE to food allergens (cow's milk, hen's egg, peanut, wheat, cocoa) in serum was measured using the PEIA Cap System.

The statistical analysis was performed using the STATISTICA v. 8.0 software package (StatSoft, Inc., Minneapolis, USA). Correlation of clinical and serological parameters with serum receptor levels was evaluated by Spearman rank correlation coefficients. The obtained results were considered significant at $p < 0.05$.

Results

Extrinsic type of AD (eAD) was diagnosed in 72 (73%), and intrinsic type of AD (iAD) in 30 (27%) patients. Sixty-three percent of 40 AD patients in whom SPT were performed presented positive test results (Fig. 1). In 31% of patients with AD, SPT were negative. Only 6 out of 64 patients with AD (9%) presented positive results of SPT to food allergens. In this group, positive results were observed only with extracts of celery (6 patients) and

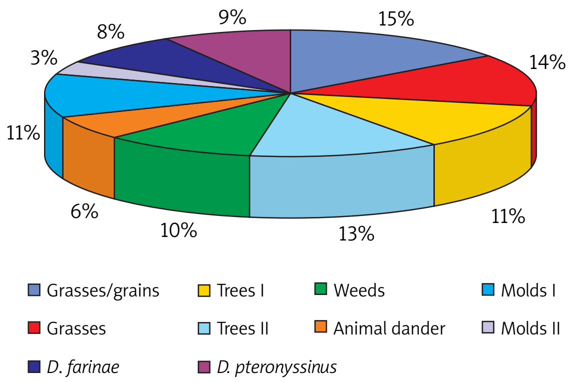


Fig. 1. Results of skin prick tests with airborne allergens in patients with AD

apple (6 patients). Furthermore, signs of OAS were reported by all 6 individuals.

Both SAFT and APT were performed in 60 children with AD below 9 years of age, thus in 58.8% of the investigated population. Positive SAFT results were observed in 3 out of 60 examined patients (5%), negative in 92% and doubtful in 3% of the group. However, positive results were observed exclusively in children below 3 years of age (37 individuals); thus in this group SAFT was positive in 8%. In 5 out of 60 examined AD patients (8%) APT was positive, in 82% negative and doubtful in 10% of the group of children with AD. However, positive results were observed exclusively in children below 5 years (50 individuals); thus in this group APT was positive in 10%.

The most common food allergens based on positive results of SAFT and APT are shown in Figs. 2 and 3.

In the investigated population of AD patients serum levels of asIgE to food allergens were determined. The spectrum of the most common food allergens recorded in SAFT and APT was confirmed by elevated levels of asIgE in serum of patients with positive test results (Table 1).

In conclusion, on the basis of the standard diagnostic procedures (SAFT, APT, SPT and asIgE), food allergy was diagnosed only in 8% of the investigated AD population. Assuming that signs of sensitization to food allergens were observed exclusively in children with AD below 5 years of age, FA was diagnosed in 16% of the population. However, it should be emphasized that subjective symptoms of FA were reported by 68% of patients with AD. Sensitization to airborne allergens was diagnosed in 39% of the examined patients with AD.

In the investigated population, the mean value of W-AZS score was 39.4 ±29.8 points (0-161 points), the mean value of pruritus 12.6 ±7.6 points (0-32 points), and the mean value of SCORAD 42.9 ±24 points (0-101 points). In the group of patients with AD and FA the mean value of W-AZS was 69.5 ±18.4 points (43.8-102.7 points), the mean values of pruritus 17.25 ±8.9 points (6-32 points), and the mean value of SCORAD 73.2 ±18 points (39.8-89 points) (Table 2). The scores of W-AZS recorded in patients with AD and FA were statistically higher in comparison with the rest of the AD group (p = 0.006) (Fig. 4), yet there

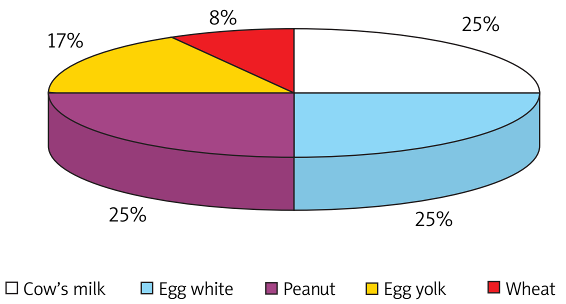


Fig. 2. Results of SAFT in children with AD

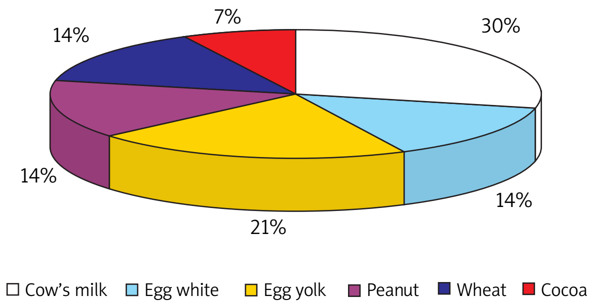


Fig. 3. Results of APT in children with AD

Table 1. Serum levels of asIgE to most common food allergens

Allergen	Elevated levels of asIgE (number of patients)	Percentage of positive results (%)	Range of concentrations [kU/l]
Cow's milk	7	28	2.31-14.2
Hen's egg	7	28	0.63-83.1
Peanut	5	20	1.06-82.9
Wheat	5	20	0.41-86.3
Cocoa	1	4	0.73-15.2

Table 2. Disease extent and severity evaluated with W-AZS and SCORAD in the investigated population of patients with AD

Group		*n*	SCORE (points)	Mean ± SD	Median	Minimal value	Maximal value
Extrinsic atopic dermatitis	eAD	72	W-AZS	47.8 ±31.2	43.5	0	161
			PRURITUS	14.5 ±7.9	14	0	32
			SCORAD	50.4 ±23.6	47.7	0	101
	AD and FA	8	W-AZS	69.47 ±18.4	70.8	43.8	102.7
			PRURITUS	17.25 ±8.9	15.5	6	32
			SCORAD	73.2 ±18	81.2	39.8	89
	AD and AA	64	W-AZS	45.1 ±31.5	37.7	0	87.9
			PRURITUS	14.2 ±7.8	14	0	32
			SCORAD	47.6 ±22.8	46.3	0	101
	AD and OAS	6	W-AZS	76.3 ±43.6	77.05	18.5	135.6
			PRURITUS	18 ±7.3	19.5	6	26
			SCORAD	61.6 ±28.7	67.5	20.6	92
Intrinsic atopic dermatitis		30	W-AZS	19.2 ±10.6	17.9	4.4	57.8
			PRURITUS	8.2 ±4.2	6	0	21
			SCORAD	24.8 ±13.05	23.9	4.4	60.1

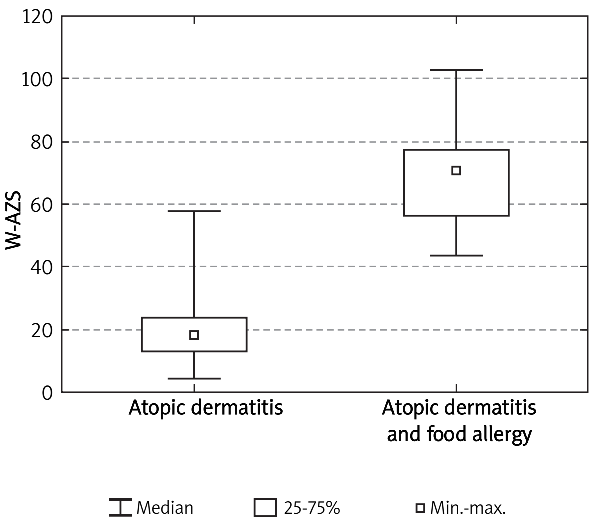
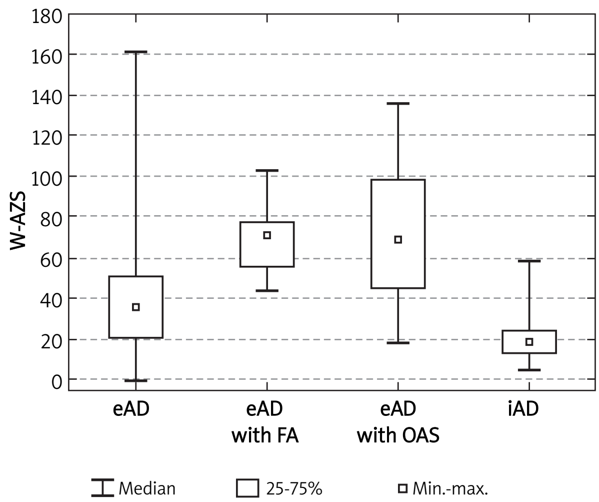


Fig. 4. Significant difference between W-AZS values in patients with AD and FA in comparison with the rest of the AD group (*p* = 0.006)



AD – atopic dermatitis, FA – food allergy, OAS – oral allergy syndrome, eAD – extrinsic type of AD, iAD – intrinsic type of AD

Fig. 5. W-AZS values in the investigated groups of AD patients

was no difference in the recorded values of pruritus between the two groups (*p* = 0.367). Moreover, the W-AZS scores in AD patients with FA were significantly higher compared with the group with AD and airborne allergy (*p* = 0.041), and the iAD group (*p* = 0) (Fig. 5). Furthermore, pruritus scores in patients with AD and FA were statistically higher only in comparison with the iAD group (*p* = 0.01), but the difference was not significant compared with AD patients with airborne allergy (*p* = 1.0). In the group of patients with AD and coexistent signs of OAS, the mean value of W-AZS was 76.3 ±43.6 points (18.5-135.6 points), the mean value of pruritus 18 ±7.3 points (6-26 points), and the mean value of SCORAD 61.6 ±28.7 points (20.6-92 points) (Table 2). W-AZS scores recorded in

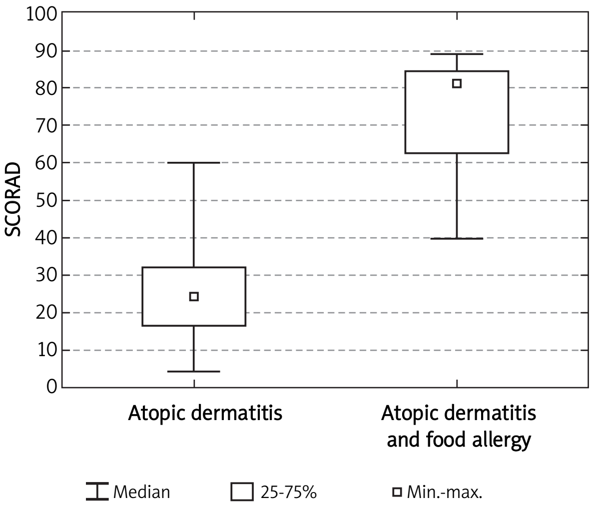


Fig. 6. Significant difference between SCORAD values in patients with AD and FA in comparison with the rest of the AD group (p = 0.006)

patients with AD and OAS were statistically higher in comparison with the iAD group (p = 0), and patients with AD and airborne allergy (p = 0.015), yet compared to patients with AD and FA no significant difference was found (p = 1.0). Moreover, in patients with AD and OAS the values of pruritus were significantly higher in comparison with iAD patients (p = 0), and AD patients with airborne allergy (p = 0.041), yet compared to patients with AD and FA no significant difference was found (p = 1.0).

Similarly, the SCORAD values were significantly higher in patients with AD and FA in comparison with the rest of the AD group (p = 0.005) and group (p = 0.005). Although the W-AZS scores were significantly higher in AD patients with FA in comparison with AD patients with airborne allergy, we did not observe a similar relationship with the use of SCORAD (p = 0.054) (Fig. 6).

Moreover, patients with AD and OAS presented significantly higher scores of SCORAD in comparison with the iAD group (p = 0), yet no statistically significant difference compared to AD patients with FA (p = 1.0) and AD patients with airborne allergy (p = 0.61).

Discussion

Two independent evaluation systems were used in this study in order to assess the clinical skin inflammation extent and severity in the investigated population of patients with AD: SCORAD and W-AZS. In our opinion, SCORAD is a useful score either when initial assessment of an AD patient is necessary or fast evaluation is required in order to monitor the efficacy of the treatment [27]. The W-AZS on the other hand is a more complex and accurate score, expressing the actual general condition of a patient with AD [28]. The SCORAD is based on evaluation of only one representative area of the skin, while W-AZS enables evaluation of every area of the patient's skin, providing more thorough clinical information, as it distinguishes between acute and chronic inflammatory lesions [28]. The essential advantage of W-AZS is a parallel evaluation of subjective symptoms reported by AD patients, such as intensity of pruritus and sleep disorders, which influence the quality of life significantly [28].

Clinical evaluation of AD patients with the W-AZS score revealed that disease severity was described as mild in 72%, moderate in 23% and severe in 5% of the population, whereas with the SCORAD index 35% of the recruited AD population presented mild, 33% moderate, 30% severe disease, and 2% signs of erythroderma. Two individuals evaluated as erythrodermic with the SCORAD index (respectively 92 and 101 points) presented chronic, inflammatory skin lesions observed in the course of relapsing atopic dermatitis. Disease extent and severity assessed with W-AZS were respectively 135 points and 161 points, indicating severe AD, but not erythroderma (scores above 181 points).

Significantly higher values of the disease extent and severity in patients with AD and FA in comparison with the rest of the investigated AD group as well as the AD group with airborne allergy and the iAD group may justify the role of food allergens in the development of inflammatory lesions in the skin, but only in the population of children. In the evaluated population, positive test results with food allergens were recorded exclusively in children below 5 years. This is comparable with the literature data, as it was confirmed that FA may play some role in the induction of inflammation in the skin in the population of the youngest AD patients. It was also proved that most children outgrow FA, although they still suffer from AD, often presenting signs of airborne sensitization instead [9, 10, 35-37].

The SAFT with native food allergens is considered a very useful diagnostic tool in children below 4 years when immediate reactions after consumption of food are suspected. According to many published results, most children with a history develop tolerance to sensitizing agents by the age of 9 years. Although SAFT is usually recommended in children below 4 years, the test was performed in the evaluated population in all children with AD below 9 years, in order to check the usefulness of the test in older children [29, 33]. The APT with native food allergens is regarded as a very useful diagnostic tool in patients with the suspicion of late reaction after consumption of foods [30-33]. The APT may be performed at every age, although it is usually useful in children with suspected FA. Although many tests are available to diagnose FA, the double blind placebo controlled food challenge (DBPCFC) remains a gold standard in the diagnostic approach of food hypersensitivity [21, 22]. In this study, current experience of numerous researchers working in the field of FA was taken into consideration. Thus evaluation of serum levels of asIgE together with SPT and SAFT/APT with food allergens reduces the need to perform DBPCFC. Whereas DBPCFC is a procedure difficult to perform and interpret, it was demonstrated that SPT and SAFT/APT with determination of asIgE show a very high positive predictive value (PPV) [33-37].

Among the recruited population of AD patients, 68% reported subjective signs of food hypersensitivity. However, based on the diagnostic procedures (SAFT, APT, SPT, asIgE) FA was diagnosed only in 8% of them. Moreover, FA was diagnosed exclusively in children below 5 years, and in this group 16% of them were affected. It is significant that 62% of the investigated population admitted self-treatment with diets without a doctor's advice, usually based on elimination of suspected foods. Among patients with AD and a history of elimination diets, only 41% reported improvement of the disease severity. The relatively high percentage of AD patients reporting reduction of disease severity on elimination diets compared with low incidence of FA in the investigated population is easy to explain. Numerous studies have shown that foods reported by patients or their parents as potential allergens differ significantly from the profile of the most common food allergens confirmed in laboratory findings [38, 39]. As an example, respondents usually list fruits (citrus fruits), milk or chocolate, while the most common food allergens are CMP, hen's egg, cocoa, wheat, soy, fish and crustaceans. Citrus fruit, strawberries, chocolate and cheese contain vast amounts of histamine, tyramine and dopamine. These mediators transmit the itching sensation and may induce pseudoallergic symptoms after consumption without involvement of IgE-dependent mechanisms. Thus a decrease in the severity of pruritus may be observed during elimination of histamine-rich foods.

A significant disproportion between subjective symptoms of FA and the incidence of FA based on standard diagnostic procedures has been observed by many scientists studying the issue of FA [38, 39]. The majority of researchers report, however, that FA may affect between 25 and 50% of children with moderate to severe form of AD [8-10, 12, 14]. In the investigated population, predominance of mild to moderate form of AD was observed, which explains the relatively low percentage of individuals with FA, diagnosed in 16% of children. In fact, individuals included in our study were usually patients with mild or moderate form of AD, as they were able to stop the treatment with antihistamines at least 2 weeks prior to diagnostic procedures.

It should be emphasized that we assumed a scheme of diagnostic procedures in FA, as recommended by many researchers, based on the exclusion of FA in case of negative test results (SPT, SAFT, APT) and undetectable serum levels of asIgE. Nevertheless, DBPCFC remains a gold standard in the diagnostic approach of FA, as it reflects the natural way of consumed, digested and absorbed food [18, 19, 32]. Thus, positive results of DBPCFC are likely to occur in patients with negative test results, which may decrease the incidence of FA in the investigated AD population.

The evaluated population of AD patients showed high incidence of airborne allergy, as 63% of 64 patients above 4 years of age presented positive SPT results to at least one of the allergens. This confirms the important role of airborne sensitization in the development and course of AD. Numerous studies have shown that airborne allergens stimulate atopic inflammation both in the respiratory system and in the skin. Thus some AD patients report seasonal aggravation of the disease after exposure to inhalant allergens, with no coexistent signs of allergic rhinitis, conjunctivitis or asthma [40].

Oral allergy syndrome, related to cross-reactivity to food antigens in patients allergic to inhalant allergens, is a common disorder, that was observed in 9% of the investigated AD population. Positive results of SPT with food extracts were observed only in patients with AD and coexistent allergic rhinitis and OAS. In contrast, the control group of patients with allergic rhinitis reported OAS in 40% of cases. The most common food allergens among AD patients with AR and OAS, as well as in the control group with AR, were celery and apple. Celery and apple are essential diet compounds in Europe, whereas birch and mugwort pollens are the main airborne allergens in our climate [17, 25]. The main allergens of birch and mugwort pollens are very similar to antigens of common fruits and vegetables, which explains the high incidence of cross-reactions to food in patients with airborne allergy.

Summarizing the conclusions of the discussion, reports of AD patients on food hypersensitivity and the influence of food allergens on the clinical course of disease should not be overestimated. Quite the opposite, airborne allergy may both influence disease severity significantly and induce signs of food hypersensitivity due to the risk of cross-reactions. Significantly higher scores of W-AZS and SCORAD in patients with AD and IgE-dependent FA may indicate the role of food allergens in the course of AD, but exclusively in patients below 5 years of age.

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