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The Severity of Atopic Dermatitis in Chidren and the Role of Hypersensitivity to Food Allergens in its Occurrence

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Background: The SCORAD index is most often used to assess the severity of atopic dermatitis (AD). Hypersensitivity to food allergens is found in up to 60% of children with moderate to severe forms of the disorder and it is a significant cause of intensification of skin changes.

Aim: The study was to assess the severity of AD and the presence of hypersensitivity to food allergen.

Methods: The study comprised 114 children (56 boys and 58 girls) aged from 1.5 months to 14.9 years, with diagnosed AD according to Hanifin and Rajka's criteria. The severity of the illness was assessed by the SCORAD index and the following were analysed to recognize hypersensitivity to food allergens: anamnesis data, total IgE antibodies, specific IgE antibodies and the results of the skin prick test (SPT) for food allergens.

Results: 61.4% of children had a moderate form of the illness, the median SCORAD index was 28.5 points. There was a significant correlation with the total SCORAD index values for: spread ($p< 0.0001$), intensity ($p<0.0001$) and subjective signs ($p<0.0001$), as well as a correlation between the parameters: spread and intensity of changes ($p < 0.0001$); spread and subjective signs ($p< 0.0001$); intensity and subjective signs ($p < 0.0001$). Hypersensitivity to food allergens was found in 28% of children tested (history of hypersensitivity to food 47.5%, high total IgE antibodies 56.1%, SPT positive 32.4%, specific IgE antibodies to food allergens 28%), and the most frequent allergens responsible were cow's milk, 12.3% and eggs in 5.3% children.

Conclusion: The most common was the moderate form of illness, and hypersensitivity to food allergens was significantly present. By removal of the responsible allergen, we can contribute to a reduction in the intensity of changes.

Keywords: *atopic dermatitis, SCORAD index, hypersensitivity to food allergens*

INTRODUCTION

Atopic dermatitis (AD) is an inflammatory, chronically relapsing, non-contagious and pruritic skin disorder, caused by a genetic predisposition (atopy), and is characterised by extremely itchy and dry skin, with typical changes, depending significantly on the age of the child and severity of the disorder [1]. In infants, the changes are oozy, with redness, vesicles and crusts mostly localized on the face, neck, body and extended parts of the extremities. After infancy the symptoms are dry on an erythematic base, with lichenification and excoriation, more commonly present on the dorsal and folded areas of the extremities [2,3].

Due to the variety in character, intensity and localization of AD changes on the one hand and the current lack of serological tests to "measure" the severity of AD on the other, assessment of the severity of the disorder is primarily based on signs and symptoms [4]. For the most objective and even assessment of the severity of the disorder, a large number of point systems have been developed, but the one used most often in clinical practice is the Severity scoring of atopic dermatitis index (SCORAD index), which includes six objective and two subjective parameters [5].

In 45% of affected children AD changes appear in the first six months of life, in about 60% children during the first year and up to the age of 5 the changes appear in about 85% of affected children [6,7]. The number of children affected with AD has been rising over the last few decades, and is now at about 10-21% in developed countries [7,8].

Pathogenesis of AD involves a complex interaction between genetic background, skin barrier defects, abnormalities of the immune system of the organism, the immune response of the skin and environmental influences (aeroallergens, food allergens and irritants) [9,10]. It has been shown that filagrin is the first really strong identified a genetic factor in the occurrance AD. Filagrin is protein with a key role in

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Competing interests
The authors declare no competing interests.

Table 1. Parameters of SCORAD index

Parameters of SCORAD index			
	The spread of changes (A)	**Intensity of changes (B)**	**Subjective signes (C)**
In a front and behind area:	head neck upper extremities trunk genitals lower extremities	eritema edema/papula krusta excoriation lichenification excoriations dry skin	scratching interrupted sleep (due to scratching theprevious three days and nights)

the formation to maintain the efficiency of the skin barrier as protection against environmental influences. The strong association between genetic barrier defects and environmental insults to the barrier, suggests that epidermal barrier dysfunction is a primary event in the development of AD [11]. Compromised skin barrier is the cause increased transepidermal penetration of environmental allergens, increasing inflammation and sensitivity [12,13]. The influence of single constituents from the environment or food allergens might not have a direct effect on the immune response but rather act in an epigenetic form, meaning that changes in gene expression inheritable over several generations [14]. Thereby these modifications influence the fetal epigenome already during the gestational phase in utero and play an important role in the fetal basis of children disease susceptibility [15].

Hypersensitivity to food allergens is a disorder characterized excessive and abnormal immune reaction to certain food proteins. There is still a subject of study, whether hypersensitivity to food allergens etiological factor in the occurrence of AD, or a factor that aggravates the situation, or a factor associated with AD with a slightly higher expression in children with atopic predisposition [16].

Significant problem in children with AD is hypersensitivity to food allergens, since it is a "trigger" for the appearance of the first but also an intensification of existing skin changes [17]. It is present in 40%-60% infants and children with moderate to severe forms of AD [18-22]. For most children with AD (>90% of cases) who have hypersensitivity to food allergens, the allergens responsible are found in: cow's milk, eggs, wheat flour, soya or peanuts [17]. Relation between food allergens and severity of the disorder is well know, there are reports where hypersensitivity to food allergens was found in 13.5% of children with mild form of AD, in 37.2% of children with moderate form, and in 36.4% of children with severe form of disease. The most common allergens responsible for hypersensitivity were milk, egg and peanuts [6,23].

The recognition that hypersensitivity to food allergens has an important role in the occurrence and maintenance of pathological processes in the skin of children with AD indicates the importance of recognizing the allergens responsible, so that by avoiding them a contribution could be made to reducing the intensity of changes, less exacerbation and longer remission of the disorder.

Therefore the aim of this study was to assess the severity of AD in children and assess the presence of hypersensitivity to food allergens.

METHOD

A prospective study was conducted at the Clinic for children's diseases at University Clinical Center (UCC) in Tuzla in the period from 1 December 2009 to 30 June 2010. The criteria for inclusion were: satisfying at least three major and three minor criteria according to the Hanifin and Rajka [24] diagnostic criteria for AD, that the children were aged up to 15 on the day of testing. Criteria for exclusion were: not meeting the diagnostic criteria, age above 15 years, the use of antihistamines in the past 5 days, use of corticosteroids (systemic or local) in the previous 4 weeks, acute and/or chronic disorder with no atopic basis, an associated systemic disorder, and the parents' refusal for the child to take part in the study. 114 children met the study criteria.

The following were analysed: the age and sex of the child, the age of the child when the first signs of AD appeared, the severity of the disorder, the form of nutrition, data on hypersensitivity to foods allergens, about atopy in the personal or family history, the total IgE antibody values, specific IgE antibodies to food allergens, and the results of the skin prick test (SPT) for food allergens.

For evaluation severity of the disorder SCORAD index was used. (Table 1.)

We assessed: (A) the spread of changes and it was expressed in a range of 0-100. Intensity of changes (B) was presented by a scale of 0-3 where 0 indicated absence of changes, 1 minor changes, 2 moderate changes and 3 intense changes.

The subjective signs (C) was presented by a scale from 1-10 where 0 signifies "never better" and 10 "never worse". The child (if it was an older child) or the child's caretaker expressed the intensity of the subjective signs. The values of the SCORAD index were calculated according to the formula A/5+7B/2+C. The maximum SCORAD index value was 103. According to the SCORAD index values the severity of the disorder was assessed as: mild (<15 points), moderate (15-40 points) or severe (>40 points) [5].

Table 2. Presence of diagnostic criteria for atopic dermatitis

Diagnostic criteria for atopic dermatitis			n	(%)
Major criteria		Itchy skin and scratching	109	95.6
		Typical localized changes	98	85.9
		Chronic skin changes	88	77.2
		Positive personal history for atopic Disorder	23	20.2
		Positive family history for atopic disorder	34	29.8
Minor Criteria	**Skin symptoms**	Dry skin	103	90.3
		Paleness/erthyma of face	53	46.5
		Eczema changes around nipples	-	-
		Repeated skin infections	20	17.5
		Intolerance of wool	49	42.9
		White dermographism	17	14.9
		Hyperlinearity of palms/keratosis	11	9.6
		Pityriasis alba	3	2.63
		Cheilitis	24	21.0
		Non-specific dermatitis on hands/feet	14	12.3
		Scratching due to sweating	54	47.4
		Perifolicular accentuation	11	9.6
	Non-skin symptoms	Early age of appearance of changes	92	80.7
		High total IgE values	64	56.1
		Deterioration caused by emotional factors	94	82.4
		Deterioration caused by environmental Factors	31	27.2
		Food intolerance	54	47.4
		Type I skin hyper-reactivity	45	39.5
	Eye symptoms	Orbital dark rings	24	21.0
		Dennie Morgan fold	2	1.7
		Cataracts	-	-
		Recurrent conjunctivitis	19	16.7
		Keratoconus	-	-

Testing for food allergens, by the SPT, was performed in the Allergy Testing Department of the Clinic for children's diseases at UCC in Tuzla. The testing was carried out for groups of food allergens (cow's milk, eggs, flour, meat I and II, fruit I, II and III, vegetables I and II) using dialyzed extracts of allergens in a solution of a mixture of 50% glycerol solution in puffed saline solution (Zagreb Immunological Institute, Croatia). Urtica of >3mm were taken as a positive result of the test.

Blood for determination of total IgE antibody values and specific IgE antibodies to food allergens was taken by the standard procedure and analysed at the Polyclinic for Laboratory Diagnostics, Immunology Department at UCC in Tuzla. Blood samples were centrifuged at a speed of 2,000 revs a minute for 10 minutes. To determine total IgE antibodies, samples were analysed within 24 hours after taking the sample, by the immunonephelometry, by nephelometer (Dade Behring, Marburg, Germany). Total IgE antibody values = 0-100 IU/ml were considered normal.

To determine specific IgE antibodies to food allergens (the six most common allergens: cow's milk, eggs, flour, soya, peanuts and fish, allergens to which children had a positive SPT and food allergens for which there was a suspicion from their medical history that they were responsible for hypersensitivity), the separated sera was stored at -80°C, until it was processed for determination from all samples. The testing was performed using the ELISA method (Enzyme Linked ImmunoSorbent Assay), with Hy Tec 288 Plus apparatus, Agilent Technologies Company, Biomedica. Values >0.35 IU/ml were taken to be positive.

For this research we had the consent of the Ethics Committee of University Clinical Center in Tuzla number 01/ 1-37-492/10.

STATISTICAL ANALYSIS

Statistical analysis of the data was performed using the biomedical software "MedCalc for Windows version 114.4" Numerical data were shown as central tendency and appropriate dispersion measures. Variables with distorted distribution are shown by the median as the measure of the central value, and the interquartile range.

The significance of the correlation between the variables was tested using Spearman's rank coefficient correlation. Values of $p<0.05$ were considered to be statistically significant.

Table 3. Form of disorder according to SCORAD index values

SCORAD index values	Form of disorder		
	Mild form (n = 23)	Moderate form (n = 70)	Severe form (n = 21)
Median	11.36	28.5	70.86
Interquartile range	11.0-13.0	22-35.9	60.8-78
Minimal values	4.7	16	39
Maximum values	14.8	39	102

RESULTS

In the period from 1 December 2009 to 30 June 2010 in the specialist clinic and/or the Department of Allergology, Immunology and Rheumatology of Clinic for children's diseases at UCC in Tuzla, of 646 children examined and/or hospitalized, atopic dermatitis (AD) was found in 126/646 (19.5%) children. 12 children with AD were excluded from the study: seven had used antihistamines, three children had received systemic corticosteroids, one child had an associated systemic disorder, and for one children written consent to be included in the study was not given.

The median age of the 114 children with AD examined was 27.5 months (interquartile range: 12.5-66 months) with a minimum of 1.4 months and maximum of 14.9 years. The sex distribution was 56 (49.1%) boys and 58 (50.8%) girls. The presence of the diagnostic criteria (Hanifin and Rajka) is shown in Table 2.

A positive family history for atopic disorder was found in 29.8% of the children examined with AD and 23/114 (20.2%) of the children examined with AD had an atopic disorder in their personal history (7 had asthma and 16 allergic rhinitis). Changes at typical locations for AD were found in 85.9% of children examined with AD (face: 37.7%, face and skin folds on neck 9.6%, face and upper extremities 22.8%, lower extremities 14.9% and trunk 10.5%).

SCORAD index values in the examined children with AD had a median of 28.5 points (interquartile ranges 17.4-38 points) with a minimum of 4.7 and maximum of 102.8 points. According to the SCORAD index values, an assessment was made of the severity of the disorder in the children examined with AD, as mild, moderate and severe forms (Table 3). The most common was the moderate form, found in 61.4% of children examined with AD.

The median values of distribution of changes in the children examined with AD was 21 points (interquartile ranges: 11-35), with a minimum of 5 and a maximum of 98 points, whilst the value of the parameter of intensity of changes had a median of 5 points (interquartile range: 3-7) with a minimum of 1 and a maximum of 17 points. For the parameter of subjective signs in the children examined with AD, the median was 6 (interquartile range: 3-10) with a minimum of 1 and a maximum of 19 points.

The connection between some parameters was positive and very high, and statistically significant, according to the total SCORAD index scores: spread of changes ($r = 0.79$, $p< 0.0001$; 95% CI: 0.71- 0.85), intensity of changes ($r = 0.95$, $p<0.0001$; 95%CI: 0.93-0.97) and subjective signs ($r = 0.85$, $p<0.0001$; 95%CI: 0.79-0.89).

When analysing the connection between individual parameters of the SCORAD index, in the children examined with AD, we found a positive, significant correlation for: spread and intensity of AD changes ($r = 0.67$, $p < 0.0001$; 95%CI: 0.55-0.67); spread and subjective signs ($r = 0.63$, $p< 0.0001$; 95%CI: 0.51-0.73), as well as for the parameters of intensity of changes and subjective signs ($r = 0.76$, $p < 0.0001$; 95%CI: 0.67-0.82).

When testing the occurrence of hypersensitivity to

Table 3. Numerical amount of positive and negative results of parameters to assess hypersensitivity to food allergens

Parameters of hypersensitivity to food allergens	Children with atopic dermatitis							
	With hypersensitivity on food allergens (n=32)				Without hypersensitivity on food allergens (n=82)			
	present		absentee		present		absentee	
	n	%	n	%	n	%	n	%
History of food intolerance	32	28.1	-	-	22	19.3	60	52.6
Total IgE* antibodies	32	28.1	-	-	32	28.1	50	43.8
SPT on food allergens**	32	28.1	-	-	5	4.3	77	67.6
Specific IgE antibodies on food allergens	32	28.1	-	-	-	-	82	71.9

food allergens in the children examined with AD, we found that the median age of the children when the first AD changes appeared was 6 months (interquartile range: 3-12.5, with a minimum of 0.5 and maximum of 48 months). The median age of the children when other food was introduced (food apart from mother's milk) was also six months (interquartile range: 4.8-6 months) with a minimum of 0 and a maximum of 9 months, and we found a positive, weak (r = 0.19) but statistically significant correlation (p = 0.03, with 95%CI: 0.01-0.36) between the age of the appearance of the first changes and the introduction of other food into the diet of the children examined with AD.

Positive history of food intolerance is found in 54/114 (47.5%) of examined children with AD, while elevated levels of total IgE antibodies had 64/114 (56.1%) children with AD the median value of the total IgE antibodies was 288.5 IU/ml (interquartile ranges: 42-730 IU/ml) with a minimum of 7.6 and maximum of 3280 IU/ml. Positive SPT on food allergens had 32.4%, a and specific IgE antibodies on food allergens 28.1% of examined children with AD. The SPT for food allergens in the children examined with AD was most often positive for cow's milk (n=17) and eggs (n=8), then fruit III (n=5), vegetables II (n=4), flour (n=3). The most frequent positive specific IgE antibodies to food allergens were for: cow's milk (n=14) and eggs (n=6), and then peanuts (n=4), peas (n=3), soya (n=3), hazelnuts (n=1), and tomatoes (n=1).

Hypersensitivity to food allergens has been demonstrated in 32/114 (28%) of the examined children with AD and these children had a positive history of food intolerance, elevated levels of total IgE antibodies, positive SPT on food allergens and positive specific antibiodies on food allergens, while for 82/114 (71.9%) children we did not prove hypersensitivity to food allergens.

The numerical relationship between positive and negative findings of parameters for assessing the presence of hypersensitivity on food allergens in children with AD is shown in Table 3.

Investigated children with AD-om which have proven hypersensitivity to food allergens (32/114), was the median age of 31.25 months, while the age of children for whom we have not proven hypersensitivity to food allergens (82/114) had a median of 26 months, and we did not find statistically significant differences for age of children with AD-om between this two groups (p=0.15). Analyzing the gender structure, we found that the 32/114 children with sensitization to food allergens was 11 (34.4%) boys and 21 girls (65.6%), while in the group of children without proven hypersensitivity to food allergens (82/114) were 45 (65.85%) boys and 37 (45.1%) girls, with a borderline significant difference in gender (p=0.04).

DISCUSSION

In a time period of 7 months, using the SCORAD index (analysing the SCORAD index parameters, their connection to the total SCORAD index scores, and their connections with each other), we assessed the severity of AD in children, and the presence of hypersensitivity to food allergens in the children examined with AD on the basis of medical history data on hypersensitivity to food, total IgE antibody values, specific IgE antibodies to food allergens, and the results of skin prick tests (SPT).

Analysing the individual diagnostic criteria for AD, we found an early age of the appearance of the first changes (before the age of 2) in 80.7% of the children examined with AD and the median age of the children when the first changes appeared was 6 months, with an interquartile range of 3-12.5 months. Our results are in line with references from the literature. AD rarely appears in the first six weeks from birth, at about 6 months it occurs in 45-65% of children, whilst it begins in about 75% of the children in the first year of life [25,6,7].

Changes at the typical locations for AD were found in a significant number of the children examined with AD, 85.9%, and they were most often on the face, 37.7%, and the face and upper extremities in 22.8%, as expected, in accordance with the data in the literature, and according to age of the children examined with AD (median age 27.5 months, interquartile range: 12.5-66 months). Namely, the localization and form of changes of AD depends on the age of the child, so in infants the most common places are: the face (c. 80%), auricles, retroauricular grooves, skin folds on the neck, the scalp, the trunk and the extensive areas of the extremities. After the infant period, the lips and perioral parts are dry and cracked, sometimes with completely expressed cheilitis, changes are more common on the dorsal areas of the extremities, typically affecting the creased surfaces [2, 9].

The dominant symptom of AD is itchy skin, which means that children with AD are disturbed, they cry more, and their sleep is restless and interrupted [26,27]. And our results are consistent with these, the most common major criteria in our study was also itchy skin, in 95.6% of children examined with AD, and we also found a significant connection between the parameters of subjective signs (scratching and broken sleep due to scratching) with the total SCORAD index values.

Atopic dermatitis is the earliest manifestation of a series of atopic disorders, and is followed by allergic rhinitis and asthma. About 40% of children with AD later develop asthma, and the risk is more than 50% in children with hypersensitivity to food allergens (most often eggs) [28,18,19]. Our results are somewhat different. A family history of atopic disorders was found in 29.8% of children examined with AD and associated atopic disorders in 20.2% children: 7 had asthma, and 16 had allergic rhinitis.

In our study in the children examined with AD, the most common was the moderate form of the disorder (in 61.4% of the children examined with AD) with a median SCORAD index value of 28.5 points. Our results are similar to other researchers who report that the moderate and severe forms of the disorder are most common, so the median SCORAD index value in the research by Pourpak et al [29] was 60.7 points Murat-

Sušić et al [30] found SCORAD index values ranging from 16-83 points. The SCORAD index values in children with AD in the research by Wahn et al [31] had a range of 5-59 points, and the most common was the moderate form, as it was in the research by Carmi et al [32], where the moderate form of the disorder was dominant, with SCORAD index values in the ranges of 5-70 points and a median value of (31.6±17.0) points.

The correlation between the SCORAD index parameters, in children examined with AD, according to the total SCORAD index values, and the correlation between individual parameters, was positive, high and statistically significant. Our results are similar to other researchers. In the research by Pucci et al [33] a significant correlation is pointed out between the parameters as well as the parameters and the total SCORAD index values. Willemsen et al [34] however found a significant correlation between the intensity of the changes and the subjective signs, but a weak correlation between the spread of changes with the SCORAD index values.

There is an increasing amount of clinical and laboratory evidence that hypersensitivity to food allergens plays an important role in the pathogenesis of AD, with prevalence in a wide range from 20% to 60% of children with AD, depending on the age of the child but also the severity of the disorder [21, 22, 10, 35].

Exposure to food allergens in the first months of life may contribute to sensitising children, so hypersensitivity to the proteins in cow's milk and eggs is common in children (up to 69%) with AD in the first three years of life [36,37,16]. Our results are consistent with the above. In our study of children examined with AD, the age of the first appearance of AD and the age of introduction of other food (apart from mother's milk) had a median of 6 months, with weak (r=0.19) but statistically significant correlation (p=0.03). We are the same as the other researchers as the most recognized food allergens found cow's milk and egg.Illi et al [6] emphasise that hypersensitivity to food allergens (primarily cow's milk and eggs) has a significant effect on the severity of the disorder and is responsible for the persistence of symptoms in childhood. On the other hand, according to some authors, there is no certain evidence that delaying the introduction of other food after the age of six months has any effect on the occurrence of AD or atopic sensations in the first two years of life [20,38].

We found hypersensitivity to food allergens in 28% of the children examined with AD, and our results are similar to the results of Eigenmann et al [16] who noticed hypersensitivity in their research to food allergens in 33.8% of children with AD. On the other hand our results are different from the results of Garcia et al [35] who found hypersensitivity to food allergies in as many as 61% of children with AD included in their research.

The most frequent food allergens responsible for hypersensitivity in our study in the children examined with AD were cow's milk and eggs. Our results are in line with the result of studies undertaken earlier in which it was shown that in children with AD who are hypersensitive to food allergens, in about 90% of cases the allergens responsible are cow's milk, eggs and then flour and soya, peanuts and fish [17,36,37,16]. The results of research by Pourpak et al [29] are similar, as they found the most common food allergens responsible for hypersensitivity in children with AD were cow's milk, tomatoes and eggs, and to a slightly lesser extent nuts and flour.

CONCLUSION

The most common form of the disorder was moderate in children examined with AD, with the significant presence of food allergens. The food allergens recognized are probably an important factor in the occurrence and maintenance of the pathological processes on the skin of children examined with AD. Discovering the responsible allergens (a thorough history of hypersensitivity to food, finding the total IgE antibodies, the SPT and finding the specific IgE antibodies for food allergens) and avoiding them can be mitigated, if not completely cut the intensity of changes, reducing the frequency of exacerbation and try to achieve longer remission of the disorder.

REFERENCES

1. De Benedetto A. Atopic dermatitis: a disease caused by innate immune defects? J Invest Dermatol 2009; 129: 14-30. http://dx.doi.org/10.1038/jid.2008.259 PMid:19078985

2. Abels C, Proksch E.Therapy of atopic dermatitis. Hautarzt 2006; 57: 711-23. http://dx.doi.org/10.1007/s00105-006-1176-x PMid:16816954

3. Leung DYM, Rhodes AR, Geha RS, Schneider L, Ring J. Atopic dermatitis (atopic eczema). In: Fitzpatrick TB, Eisen AZ, Wolff K, Freedberg IM, Austen KF (eds). Dermatology in general medicine. New York: McGraw Hill 1993; 1543-64.

4. Charman C, Chambers C, Williams H. Measuring Atopic Dermatitis Severity in Randomized Controlled Clinical Trials: What Exactly Are We Measuring? J Inves Dermatol 2003; 120: 932–41. http://dx.doi.org/10.1046/j.1523-1747.2003.12251.x PMid:12787117

5. Anonymus. European Task Force on Atopic Dermatitis Severity scoring of atopic dermatitis: the SCORAD index. Dermatology 1993; 186: 23-31. PMid:8435513

6. Illi S, von Mutius E, Lau S, Nickel R, Gruber C, Niggemann B. The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. J Allergy Clin Immunol 2004;113: 925–31. http://dx.doi.org/10.1016/j.jaci.2004.01.778 PMid:15131576

7. Ozkaya E. Adult-onset atopic dermatitis. J Am Acad Dermatol 2005; 52: 579–82. http://dx.doi.org/10.1016/j.jaad.2004.11.037 PMid:15793505

8. Diepgen TL. Is the prevalence of atopic dermatitis increasing? In: Williams HC editor. Epidemiology of Atopic Eczema. Cambridge: Cambridge University Press 2000; 96–109 http://dx.doi.org/10.1017/CBO9780511545771.009

9. Leung DY. Atopic dermatitis: new insights and opportunities for therapeutic intervention. J Allergy Clin Immunol 2000; 105: 860-76. http://dx.doi.org/10.1067/mai.2000.106484 PMid:10808164

10. Lipozencić J, Pastar Z, Marinović Kulisić S, Pavić I. Immunologic aspects of atopic dermatitis. Acta Dermatol Venereol Croatica

2009; 17(3): 226-34.

11. Cork M. Epidermal Barrier Dysfunction in Atopic Dermatitis. J Inv Dermatol 2009; 129:1892-908. http://dx.doi.org/10.1038/jid.2009.133 PMid:19494826

12. Irvine AD. Fleshing out filaggrin phenotypes. J Invest Dermatol. 2007; 127(3): 504-7. http://dx.doi.org/10.1038/sj.jid.5700695 PMid:17299430

13. Sandilands A, Smith FJ, Irvine AD, McLean WH. Filaggrin's fuller figure: a glimpse into the genetic architecture of atopic dermatitis. J Invest Dermatol 2007; 127(6): 1282-4. http://dx.doi.org/10.1038/sj.jid.5700876 PMid:17502856

14. Miller RL, Ho SM. Environmental epigenetics and asthma: current concepts and call for studies. Am J Respir Crit Care Med 2008; 177: 567–73. http://dx.doi.org/10.1164/rccm.200710-1511PP PMid:18187692 PMCid:2267336

15. Tang WY, Ho SM. Epigenetic reprogramming and imprinting in origins of disease. Rev Endocr Metab Disord 2007; 8:173–82. http://dx.doi.org/10.1007/s11154-007-9042-4 PMid:17638084

16. Eigenmann PA, Calza AM. Diagnosis of IgE-mediated food allergy among Swiss children with atopic dermatitis. Pediatr Allergy Immunol 2000; 11(2): 95-100. http://dx.doi.org/10.1034/j.1399-3038.2000.00071.x PMid:10893011

17. Burks W. Skin manifestations of food allergy. Pediatrics. 2003;111: 1617–24. PMid:12777601

18. Guillet G, Guillet MH. Natural history of sensitizations in atopic dermatitis a 3 year follow up in 250 children. Food allergy and high risk of respiratory symptoms. Arch Dermatol 1992; 28: 187-92. http://dx.doi.org/10.1001/archderm.1992.01680120059004 PMid:1739296

19. Leung DY, Boguniewicz M, Howell MD, Nomura I, Hamid QA. New insights into atopic dermatitis. J Clin Invest 2004;113: 651–7. PMid:14991059 PMCid:351324

20. Zutavern A, Brockow I, Schaaf B, et al. Timing of solid food introduction in relation to atopic dermatitis and atopic sensitization: results from a prospective birth cohort study. Pediatrics 2006; 117 (2): 401 –11. http://dx.doi.org/10.1542/peds.2004-2521 PMid:16452359

21. Niggemann B, Beyer K. Diagnostic pitfalls in food allergy in children. Allergy 2005;60: 104-7. http://dx.doi.org/10.1111/j.1398-9995.2004.00591.x PMid:15575939

22. Sampson H. Eczema and food hypersensitivity. In: Metcalfe DD, Sampson HA, Simon AR (eds). Food allergy: adverse reactions to foods and food additives. Oxford: Blackwell Science 2003; 144-57.

23. Fernandez-Benitez M. Etiological implication of food in dermatitis atopica. Allergol et Immunopathol 2002; 30 (3): 114-20.

24. Hanifin JM, Rajka G. Diagnostic fearures of atopic dermatitis. Acta Dermatol Venereol 1980; 92: 44-7.

25. Cantani A, Micera M. Natural history of cow milk allergy. An 14-year follow-up study in 115 children. Eur Rev Med Pharmacol Sci 2004; 5: 23-9.

26. Akdis CA, Akdis M, Bieber T, Bindslev-Jensen C, Boguniewicz M, Eigenmann P. Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergology and Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Report. J Allergy Clin Immunol 2006;118:152–69. http://dx.doi.org/10.1016/j.jaci.2006.03.045 PMid:16815151

27. Kristal I, Klein PA. Atopic dermatitis in infant and children. Pediatr Clin North Am 2000; 47: 877-96. http://dx.doi.org/10.1016/S0031-3955(05)70246-7

28. Gore C, Custovic A. Can we prevent allergy? Allergy 2004; 59: 151-61. http://dx.doi.org/10.1046/j.1398-9995.2003.00358.x PMid:14763927

29. Pourpak Z, Farhoudi A, Mahmoudi M, Movahedi M, Ghargozlou M, Kazemnejad A, Eslamnoor B. The role of cow milk allergy in increasing the severity of atopic dermatitis. Immunol Invest 2004; 33 (1): 69-79. http://dx.doi.org/10.1081/IMM-120027686 PMid:15015834

30. Murat –Sušić S, Lipozenčić J, Žižić V, Husar K. Serum eosinophil cationid protein in children with atopic dermatitis. Acta Dermatol Venereol Croatica 2004; 2: 117-8.

31. Wahn U, Warner J, Simons FER, de Benedictis F M, Diepgen TL, Naspitz CK, de Longueville M, Bauchau V. IgE antibody responses in young children with atopic dermatitis. Pediatr Allergy Immunol 2008; 19(4): 332-6. http://dx.doi.org/10.1111/j.1399-3038.2007.00643.x PMid:18422892

32. Carmi E, Defossez-Tribout C, Ganry O, Cene S, Tramier B, Milazzo S, Lok C. Ocular Complications of Atopic Dermatitis in Children. Acta Derm Venereol 2006; 86: 515-7. http://dx.doi.org/10.2340/00015555-0163 PMid:17106598

33. Pucci N, Novembre E, Cammarata MG, Bernardini R, Monaco MG, Calogero C, Vierucci A. Scoring atopic dermatitis in infants and young children: distinctive features of the SCORAD index. Allergy 2005; 60(1):113-6. http://dx.doi.org/10.1111/j.1398-9995.2004.00622.x PMid:15575941

34. Willemsen MG, Van Valburg RWC, Dirven-Meijer PC, Oranje AP, Van der Wouden JC, Moed H. Determining the severity of atopic dermatitis in children presenting in general practice: An easy and fast method. Dermatol Res Pract 2009 [Epub ahead of print].

35. Garcia C, El-Qutob D, Martorell A, Febrer I, Rodriguez m, Cerda JC, Felix R. Sensitization in early age to food allergens in children with atopic dermatitis. Allergol Immunopathol 2007; 35 (1): 15-20. http://dx.doi.org/10.1157/13099090 PMid:17338897

36. Kanny G. Atopic dermatitis in children and food allergy: combination or causality? Should avoidance diets be initiated? Ann Dermatol Venereol 2005; 132 (1): 90-103. http://dx.doi.org/10.1016/S0151-9638(05)86145-9

37. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. J Allergy Clin Immunol 2001; 107(5): 891-6. http://dx.doi.org/10.1067/mai.2001.114708 PMid:11344358

38. Greer FR, Sicherer SH, Burks AW. Effects of early nutritional interventions on the development of atopic disease in infants and children: The role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. Pediatrics 2008; 121(1): 183-91. http://dx.doi.org/10.1542/peds.2007-3022 PMid:18166574