The natural course of childhood atopic dermatitis: a retrospective cohort study

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Summary

Background: **Atopic dermatitis (AD) is generally considered to be the initial step of the so-called atopic march, which following steps are allergic rhinitis (AR) and asthma. There are few data about the progression of AD, including factors associated with the remission of AD in Asians and further research is needed.**

Objective: **To study the progression and factors associated with the remission of childhood AD diagnosed by pediatric dermatologists.**

Methods: **This study included 303 AD patients who visited the pediatric dermatology unit at King Chulalongkorn Memorial Hospital, Thailand, between 2002 and 2010. An interview, performed by a physician via telephone using a preformed questionnaire, was completed for 205 children.**

Results: **A total of 205 children were observed, with a median observation time of 5.2 (3.5-8.0) years, and an initial AD severity score of mild (61.0%), moderate (29.3%) and severe (9.7%). The prevalence of AD during the first two years of life was 64.4%. AD completely disappeared in 102 cases (49.8%) by the median age of 3.5 (1.5-7.8) years. Early onset and severity of AD were major determinant of prognosis. The prevalence of AR and asthma was 36.6%, and 9.3%, respectively. The risk factors associated with respiratory allergy were the onset of AD after aged two years, a family history of atopy, increased serum IgE level, and sensitization to inhalant allergens.**

Conclusions: **Half of AD had completely disappeared at preschool age. Good prognosis was mostly determined by early onset AD and mild severity. Late onset, family history of atopy and increased serum IgE level are associated with respiratory allergy.** ***(Asian Pac J Allergy Immunol 2015;33:161-8)***

Keywords: *atopic dermatitis, childhood, allergic rhinitis, asthma, food allergy, Asians*

Introduction

Atopic dermatitis (AD) is a common chronic inflammatory skin disease in children but the pathogenesis of atopic dermatitis is still not well understood. Genetics, skin barrier defects, and immune dysregulation with environmental aggravation play significant roles in disease etiology.[1,2] AD can be the initial step of the atopic march as suggested by many studies,[3-6] and according to the International Study of Asthma and Allergies in Childhood (ISSAC), the prevalence of AD, asthma and allergic rhinoconjunctivitis has been shown to be increasing worldwide, especially in areas with low prevalence in the past.[7-9] The prevalence of AD varies from country to country and is higher in wealthy nations.[9] Environmental factors, life style and stress may influence the clinical expression of the disease.[10] There is no cure for AD, but patients can outgrow the disease. While there have been many studies investigating the natural course and prevalence of AD in Europe and North America,[3-6,11,12] we need more research regarding Asian countries in order to deepen our understanding of the disease etiology and improve management and counseling of local patients. The aim of this study was to observe and document the natural course of AD diagnosed by pediatric dermatologists in an Asian population.

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Methods

Study population

The study populations consisted of children with atopic dermatitis diagnosed by pediatric dermatologists using Hanifin and Rajka (1980) criteria,[13] at King Chulalongkorn Memorial Hospital, Bangkok, Thailand. All atopic dermatitis patients, aged two months to 15 years were invited to enroll the study from 2002 to 2010. All patients were followed up in our clinics or until remission. We excluded patients that were lost from contact.

Data review from medical records included:

Clinical manifestation of atopic dermatitis, age of onset, severity of disease using SCORAD index,[14] skin lesion infections, food allergy, family and personal history of atopy and laboratory test were extracted.

1. The clinical course of AD was defined according to the following criteria:[5]
   - Complete remission: no clinical signs of atopic dermatitis exacerbation for at least 2 years
   - Intermittent: not in remission after age two years and having occasional flare ups
   - Persistent: age more than seven years at the last follow-up with flare ups at every follow-up visit
2. Family history of atopy was included when there was a report of physician-diagnosed of AD, AR, or asthma.
3. Laboratory data included absolute eosinophil count, total immunoglobulin E (IgE), specific IgE for food and aeroallergen (ImmunoCAP, Phadia laboratory, Uppsala, Sweden).
4. Development of other allergic diseases in the patients as diagnosed by a pediatric allergist or other pediatricians was also considered valid. The clinical course of other allergic diseases was defined according to the following criteria:
   - Allergic rhinitis: one or more symptoms including sneezing, or runny, or a blocked nose without a cold or the flu in the past 12 months.[7]
   - Asthma:
     After 3 months and up to 2 years of age, at least three episodes of wheezing combined with treatment with inhaled glucocorticoids without concurrent upper respiratory infection.[15]
     In older children asthmatic status was validated when at least 4 recurrent wheezing treated with inhaled glucocorticoids occurred in the past 12 months or using ISSAC questionnaire.[7,8]
   - Food sensitizations: positive specific IgE for food.
   - Probable food allergy: patients who had positive specific IgE for food and clinical evidence of AD after ingestion.

Semistructured interviews

A preformed questionnaire consisted of items regarding the clinical course of AD, atopic family history confirmed by physician, skin lesion infections, food allergy, development of other allergic diseases and current clinical condition.

After extracting data from medical records, the preformed questionnaire was used to interview parents by a physician in our clinics or by telephone calls to the patients who did not visit our clinics for more than one year or who were in remission.

Statistical analysis

Statistical analysis was performed by using SPSS 12. Categorical variables (i.e. gender, severity, prevalence of AD, AR and asthma, family history of atopy, and specific IgE) were expressed as percentages and qualitative variables (i.e., age of onset, age of remission, and total IgE) were expressed as quartiles (interquartile Q1, Q3). To compare the variables between groups, a paired *t*-test, Chi-square and ANOVA were used. To compare factors associated with remission, logistic regression analysis was used. A p value of <0.05 was considered statistically significant.

Ethics statement

This study protocol was reviewed and approved by the institutional review board (IRB) of Chulalongkorn University, Bangkok, Thailand. Informed consent was exempted by the board.

Results

A total of 205 from 303 children with atopic dermatitis had a complete clinical evaluation and an interview. Of the 205 AD children, there were 102 boys and 103 girls (Table 1). The mean follow-up time was 5.2 (3.5-8.0) years. The severity of AD using SCORAD index was mild in 125 children (61.0%), moderate in 60 children (29.3%) and severe in 20 children (9.7%). First-degree familial atopy was present in 98 children (47.8%), involving the mother in 46 patients (22.4%), father in 38 patients (18.5%), both mother and father in 10

Table 1. Factors associated with severity of atopic dermatitis

		Severity			
		Mild N=125 n (%)	**Moderate N=60 n (%)**	**Severe N=20 n (%)**	***P* -value***
SEX	Male	62 (60.8)	28 (27.5)	12 (11.8)	
	Female	63 (61.2)	32 (31.1)	8 (7.8)	0.586
Age of onset	< 2 year	81 (61.4)	39 (29.5)	12 (9.1)	
	≥2 year	44 (60.3)	21 (28.8.2)	8 (11.1)	0.911
Immunoglobulin E	Normal by age†	26 (59.1)	16 (36.4)	2 (4.5.0)	
	above normal by age	19 (30.5)	29 (46.0)	15 (23.8)	0.003**
Eosinophil	<500 /mm^3	29 (52.7)	23 (41.8)	3 (5.5)	
	≥500 /mm^3	13 (29.5)	19 (43.2)	12 (27.3)	0.002**
Family history	No family history	62(57.9)	38 (35.5)	7 (6.5)	
	Mother or Father	63 (64.3)	22 (22.4)	13 (13.3)	0.058
Specific IgE	Food sensitization	21 (36.2)	28 (48.3)	9 (15.54)	0.330
	Inhalant sensitization	7 (26.9)	13 (48.1)	6 (22.2)	0.235
History of AD infection	No history of infection	94 (69.1%)	38 (27.9%)	4 (2.9%)	
	History of infection	31 (44.9%)	22 (31.9%)	16 (23.2%)	<0.001**

**p*-value by Chi-square test

** Statistical significant at p <0.001

AD = atopic dermatitis, IgE = immunoglobulin E, IU = international unit, †reference of serum IgE level (IU/ml)[16]

patients (4.9%), and a sibling in four patients (2.0%).

Total IgE and sensitization in AD patients

All patients were invited to do blood tests for total IgE and specific IgE for food and aeroallergen. From a total of 107 cases of AD who had blood tests, the median and interquartile range (IQR, Q1, Q3) was 297 (53.6, 1465) IU/ml. Sixty-three patients (58.9%) had a total IgE level above normal for age.[16] Percentage of elevation of total IgE in patients who had persistent AD (53.1%) was significantly higher than in intermittent AD (15.6%) and in the remission group (31.3%), with a *p* -value of 0.006.

Sensitization to food allergens was observed in 42 cases (39.3%).The most common was egg white (16.1%), followed by wheat (9.3%), cow's milk protein (7.8%), shrimp (7.8%), peanut (4.9%), soy (3.4%) and fish (1.0%). Only 33 cases had a history of symptoms after ingestion, 15 cases had urticaria and 18 cases had atopic dermatitis. Patients who had positive specific IgE for food and clinical evidence of AD after ingestion were defined as probable food allergy. Fourteen of the 18 cases with food provoked AD (77.8%) were younger than two years, only four cases were older than two years. The 98 patients who did not have blood tests had no history of food allergy. The prevalence of probable food allergy was 8.8% (18 from 205 patients).

Sensitization to aeroallergens was observed in 26 cases (24.3%). The most common was house dust mite (10.2%), follow by dog dander (2.0%) and cat dander (1.0%). Sensitization to both food and aeroallergen was seen in 16 cases (14.9%).

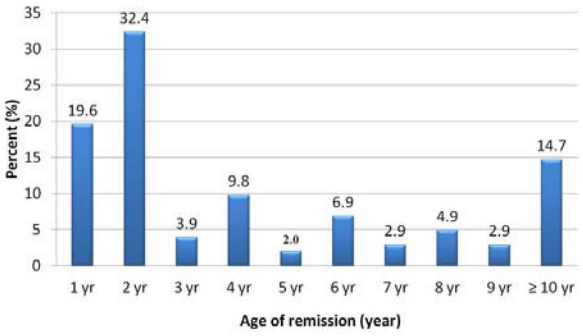

Figure 1. Age of remission in childhood atopic dermatitis

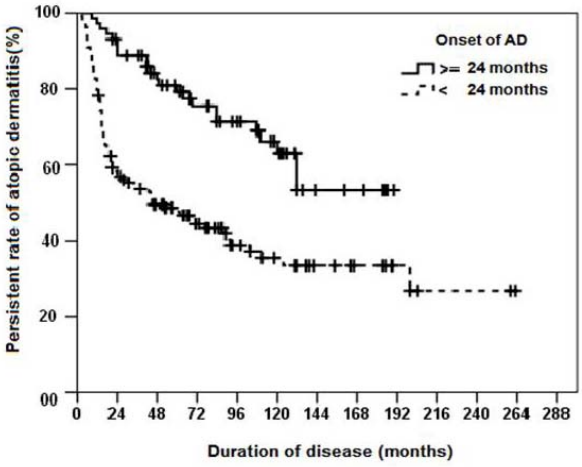

Figure 2. Graph Kaplan-Meier analysis of persistence of atopic dermatitis in patients with age of onset less than 24 months and more than 24 months. Patients who had onset after two years had significantly more prolonged clinical course than did patients who had age of onset before two years (p = 0.001)

Natural course of atopic dermatitis

Regarding the age of onset, 132 patients (64.4%) had onset of AD between two and 24 months and 54 patients (26.3%) had onset between two and five years. Only 19 patients (9.3%) had onset after five years. The median age of onset and interquartile range (IQR, Q1, Q3) was 9.5 (3.0, 36.0) months.

There were 102 cases (49.8%) that were completely in remission. Of the 102 cases, 52% were in complete remission at the age of two years, and a total of 66.7% had complete remission at the age of five years (Figure 1). The median age of remission and interquartile (Q1, Q3) range was 3.5 (1.5, 7.8) years. Patients who had onset after two years had a significantly prolonged clinical course than did patients who had age of onset before two years (p =0.001) as shown in the survival analysis (Figure 2). The average duration required for outgrowing AD in the complete remission in the group that had onset before 2 years was 107 months. The expected healing time in the case of early AD was estimated by survival analysis showing that 25% could have remission 14 months after its onset and 50% could have remission in 45 months after its onset. In the group that had onset after 2 years, the average duration required for outgrowing AD in the complete remission was 137 months.

Of patients who had onset after two years, 21.4% had intermittent and 48.5% had persistent disease while in patients with age of onset before two years, 10.4% had intermittent and 29.6% had persistent disease.

Onset of disease after the age of two years, severity of disease, increased total IgE above normal for age are risk factors of intermittent or persistent course of disease (p < 0.01) (Table 2).

Complete remission in patients with mild, moderate and severe disease occurred at a median age of remission and interquartile (Q1, Q3) range of 3.4 (1.5, 7.2), 3.5 (1.5, 7.8) and 7.0 (3.4-9.1) years, respectively.

Factors that affected the severity of disease were total IgE above normal for age, eosinophilia, and a history of AD infection (p <0.001, Table 1). Onset of diseases, family history of atopy, specific IgE either to food or inhalant antigens did not affect severity of disease (p >0.05).

History of skin lesion infections

A total of 69 from 205 cases (33.7%) had clinical signs of skin lesion infections. Patients with mild disease activity had fewer obvious skin infections (31 from 125 patients, 24.9%) than those with moderate (22 from 60 patients, 36.7%) and severe (16 from 20 patients, 80.0%), with a p-value less than 0.001. In patients with complete remission, 30.4% had a history of skin lesion infections compared to 58% of those with persistent AD, with a p- value less than 0.001.

Allergic rhinitis and asthma

From 205 patients, 63 patients (36.6%) had allergic rhinitis and 19 patients (9.3%) had asthma. Twelve patients (5.9%) that had asthma also had allergic rhinitis. Risk factors associated with AR were age of onset after the age of two years (OR = 2.32, 95% CI;1.28-4.19, p = 0.005), family history of atopy (OR = 3.12, 95% CI; 1.72-5.64, p < 0.001), total IgE above normal for age (OR = 5.18, 95% CI;

Table 2. Factor associated with intermittent and persistent AD

Variables	Remission n=102 n (%)	Intermittent/persistent n=103 n (%)	OR (95%CI)	*P* -value*
Age of onset AD				
< 2 year	81 (79.4)	54 (52.4)	1	-
≥ 2 year	21 (20.6)	49 (47.6%)	2.95 (1.62, 5.37)	<0.001**
Severity				
Mild	76 (74.5)	49 (47.6)	1	-
Moderate	25 (24.5)	35 (34.0)	2.17 (1.16, 4.06)	0.015
Severe	1 (1.0)	19 (18.4)	29.47 (3.82, 227.25)	0.001**
History of infected AD				
No history infection	81 (79.4)	55 (53.4)	1	-
History of infection	21 (20.6)	48 (46.6)	3.37 (1.82, 6.24)	<0.001**
Family history of atopy				
No family history	57 (55.9)	50 (48.5)	1	-
Either mother or father	45 (44.1)	49 (47.6)	1.24 (0.71, 2.16)	0.445
Sister/brother	0 (0)	4 (3.9)	1 (0, 1)	0.999
Total IgE (n = 107)				
Normal by age†	25 (24.5)	18 (17.5)	1	-
Above normal by age	20 (19.6)	44 (42.7)	3.06 (1.37, 6.83)	0.006**
Specific IgE (n = 107)				
Egg white	16 (15.7)	17 (16.5)	0.7 (0.31, 1.6)	0.399
Cow milk	10 (9.8)	6 (5.8)	0.38 (0.13, 1.14)	0.085
Wheat	9 (8.8)	10 (9.7)	0.78 (0.29, 2.12)	0.633
Soy	4 (3.9)	3 (2.9)	0.53 (0.11, 2.5)	0.422
Fish	1 (1.0)	1 (1.0)	0.73 (0.04, 12.05)	0.828
Shrimp	3 (2.9)	13 (12.6)	3.79 (1.01,14.22)	0.048
Peanut	3 (2.9)	7 (6.8)	1.81 (0.44, 7.44)	0.408
HDM	6 (5.9)	15 (14.6)	2.12 (0.75, 5.99)	0.156
Dog / Cat dander	2 (2)	6 (5.8)	2.35 (0.45, 12.2)	0.311

**p* -value by Logistic regression analysis

**Statistical significant at $p < 0.01$

AD = atopic dermatitis, HDM = house dust mite, IgE = immunoglobulin E, OR = odds ratio,

CI = confident interval, IU = international unit, †reference of serum IgE level.[16]

Table 3. Risk factors associated with allergic rhinitis in childhood atopic dermatitis

Variables	None n=130 n (%)	AR n=75 n (%)	OR (95%CI)	*P* -value*
Age of onset AD ≥2 year	37 (28.5)	36 (48.0)	2.32 (1.28, 4.19)	0.005**
Family history of atopy	49 (37.7)	49 (65.3)	3.12 (1.72, 5.64)	<0.001**
Increase total immunoglobulin E† (> 30 IU/L, n = 107)	27 (20.8)	37 (49.3)	5.18 (2.13, 12.56)	<0.001**
Specific IgE (n = 107)				
-Food sensitization	32 (53.3)	26 (56.5)	1.14 (0.53,2.46)	0.744
-Inhalant sensitization	10 (16.7)	17 (37)	2.93 (1.19,7.25)	0.02**

**p*-value by Logistic regression analysis

**Statistical significant at $p < 0.01$

2.13-12.56, $p < 0.001$), and specific IgE to inhalant antigen (OR = 2.93, 95% CI; 1.19-7.25, $p = 0.02$) (Table 3). The severity of AD is not associated with the development of AR ($p = 0.63$). The risk factor for the development of asthma was family history of atopy (OR = 3.4, 95% CI; 1.18-9.83, $p = 0.024$). Total IgE and sensitization were not associated with the development of asthma. The curve of AD recovery and appearance of AR and asthma are shown in Figure 3.

Discussion

This retrospective study was aimed to study the natural history in children with physician-diagnosed AD. The ISSAC study, using a questionnaire for children aged 6-7 and 13-14 years,[8] that did not include young children, found that in AD, 80% of the patients had onset before five years. There was a birth cohort study in Thailand that also used a questionnaire.[17] The problem was that not all cases identified by the ISSAC questionnaire were AD.[18] In this study, all patients were diagnosed by pediatric dermatologists and even though it was at a tertiary care center, the severity of disease was lower than in western countries.[5,6,11,12] This may be partly explained by ethnicity, lifestyle, and weather. This study was conducted in Southeast Asia which climate is hot and humid. In western countries, a cold climate will compromise skin barrier function. As we know, skin barrier function is impaired in the winter as manifested by higher transepidermal water loss values and smaller keratinocytes compare to those found in summer.[19] Exposure to cold weather may allow irritants, allergens, and microbes to penetrate into the skin and stimulate the immune system, which will aggravate eczematous skin lesions. Environment with higher humidity as in Southeastern Asian countries may cause less skin barrier dysfunction and contribute to the less disease severity.

Our patients had less familial history of atopy (47.8%) than found by studies from western countries (53-80%), but slightly more than in a study from Korea.[20] Family history of atopy was not significantly associated with severity of AD ($p = 0.058$) but was significantly associated with AR ($p < 0.001$).

A history of infected skin lesions was significantly more common in severe AD ($p < 0.001$) and correlated with persistence of disease ($p < 0.001$). *Staphylococcus aureus* plays an important role in AD patients. There are temporal shifts in the skin microbiome during disease flares.[21] Defects in the skin barrier, itching, scratching, innate immunity defects and dysregulation of the adaptive immunity facilitate colonization of *S. aureus* in AD patients. *S. aureus* infection provokes exacerbation of skin lesions by producing toxins that can stimulate immune function and itching and induce steroid resistance. *S. aureus* can produce exogenous protease that will further damage the skin barrier.[1] Early detection and treatment of skin infections will improve the control of skin inflammation and severity of disease.

The rate of complete remission in our patients at the age of five years was 66.7%, similar to the Korean study (70%). In western countries early age of onset seems to have poor prognosis.[5,6,11,12] In our

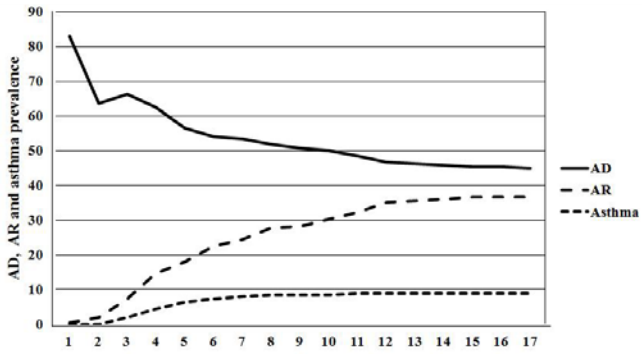

Figure 3. The curve of AD recovery and appearance of AR and asthma

study, early age of onset had better prognosis. Patients with age of onset after two years had significantly more intermittent and persistent disease course than patients with early age of onset (p <0.001). This is an interesting point that we still cannot explain, but may be because we have milder severity than in western countries. This finding still needs investigation.

Sensitization to either food or inhalant allergen did not correlate with severity of disease (p = 0.33 and 0.25, respectively). Most of the patients (14 of 18) who had positive specific IgE and clinical signs of eczematous dermatitis after ingestion were younger than two years old. Another 15 cases had urticaria after ingestion of the food.

Factors associated with intermittent or persistent course of AD were age of onset more than two years, severity of disease, history of infection, and elevated IgE. Specific IgE did not significantly correlate with disease severity but correlated with progression to allergic rhinitis. Specific IgE to food and aeroallergen correlated with urticaria/ anaphylaxis and respiratory allergy, respectively. Immediate IgE-mediated food reactions were common in moderate to severe AD patients. Food-induced eczema in AD must be proven by oral food challenge test that reveals eczematous reaction after 24 h and later.[22,23]

For progression to AR, 36.6% of AD patients developed allergic rhinitis. Risk factors associated with AR were age of onset after the age of two years, family history of atopy, total IgE above normal for age, and specific IgE to inhalant antigen. Sensitization to food was not associated with respiratory allergy. Only 9.3% of our patients developed asthma, which was lower than the incidence of asthma in the ISSAC study in Thailand (7.8% in Chiang Mai, 15% in Bangkok).[8] In the present study, AR and asthma had to be diagnosed by a physician and consequently the recorded prevalence might have been lower than in the ISSAC study. The mean follow-up time in our study was 5.2 (3.5-8.0) years. Longer follow-up time is needed to document the incidence of asthma in patients with AD.

There were several limitations associated to this study such as the fact that it was a retrospective study in tertiary care center and that 32% of cases were exclude from analysis due to follow-up loss and could not be contacted. Additionally, there is a possibility that severe patients were lost, and that clinical diagnosis and severity assessment for allergic rhinitis and asthma at the first visit may not be representative of the whole disease course.

Conclusion

This retrospective cohort study of the natural course of pediatric dermatologist-diagnosed AD in Asian patients revealed milder severity than in western countries. Early age of onset and mild severity had good prognosis. Half of patients with AD had complete remission at preschool age. Late onset, family history of atopy and increased serum IgE level were associated with respiratory allergy and progression to AR and asthma were 36.6% and 9.3% respectively.

References

1. Bieber T. Atopic dermatitis. Ann Dermatol. 2010;22:125-37.
2. Boguniewics M, Leung DY. Atopic dermatitis: a disease to altered skin barrier and immune dysregulation. Immunol Rev. 2011;242:236-56.
3. Illi S, von Mutius E, Lau S, Nickel R, Grüber C, Niggemann B, et al. 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.
4. Wuthrich B. Clinical aspects, epidemiology, and prognosis of atopic dermatitis. Ann Allergy Asthma Immunol. 1999;83:464-70.
5. Ricci G, Patrizi A, Baldi E, Menna G, Tabanelli M, Masi M. Long-term follow-up of atopic dermatitis: retrospective analysis of related risk factors and association with concomitant allergic disease. J Am Acad Dermatol. 2006;55:765-81.
6. Guatafsson D, Sjoberg O, Foucord T. Development of allergies and asthma in infants and young children with atopic dermatitis a prospective follow-up to 7 years of age. Allergy. 2003;552:40-5.
7. The International study of Asthma and Allergies in Childhood (ISAAC) steering committee. Worldwide variation in the prevalence of symptom of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. Lancet. 1998;351:1225-32.

8. Trakultivakorn M, Sangsupawanich P, Vichyanond P. Time trends of the prevalence of asthma, rhinitis and eczema in Thai children-ISAAC (International Study of Asthma and Allergies in Childhood) Phase Three. J Asthma. 2007;44:609-11.
9. Spergel JM. Epidemiology of atopic dermatitis and atopic march in children. Immunol Allergy Clin North Am. 2010;30:269-80.
10. Leung DY. New insights into atopic dermatitis: role of skin barrier and immune dysregulation. Allergol Int. 2013;62:151-61.
11. Carlsten C, Dimich-Ward H, Ferguson A, Watson W, Rousseau R, Dybuncio A, et al. Atopic dermatitis in a high-risk cohort: natural history, associated allergic outcomes, and risk factors. Ann Allergy Asthma Immunol. 2013;110:24-8.
12. Kapoor R, Menon C, Hoffstad O, Bilker W, Leclerc P, Margolis DJ. The prevalence of atopic triad in children with physician-confirmed atopic dermatitis. J Am Acad Dermatol. 2008;58:68-73.
13. Hanifin JM, Ragka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol. (Stockh).1980;92 Suppl:S44-7.
14. Kunz B, Oranje AP, Labrèze L, Stalder JF, Ring J, Taïeb A. Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. Dermatology.1997;195:10-9.
15. Wickman M, Melan E, Berglind N. Lennart Nordvall S, Almqvist C, Kull I, et al . Strategies for preventing wheezing and asthma in small children. Allergy. 2003;58:742-47.
16. Dati F, Ringel KP. Reference values for serum IgE in healthy non-atopic children and adults. Clin Chem. 1982;32:26-34.
17. Sangsupawanich P, Chongsuvivatwong V, Mo-Suwan L, Choprapawon C. Relationship between atopic dermatitis and wheeze in the first year of life: analysis of a prospective cohort of Thai children. J Investig Allergol Clin Immunol. 2007;17:292-6.
18. Czarnobilska E, Obtulowicz K, Dyga W, Spiewak R. A half of school children with 'ISAAC eczema' are ill with allergic contact dermatitis. J Eur Acad Dermatol Venereol. 2011;25:1104-7.
19. Kikuchi K, Kobayashi H, Le Fur I, Tschachler E, Tagami H. Winter season affects more severely the facial skin than the forearm skin: Comparative biophysical studies conducted in the same Japanese females in later summer and winter. Exog Dermatol. 2002;1:32–8.
20. Chung Y, Kwon JH, Kim J, Han Y, Lee SI, Ahn K. Retrospective analysis of the natural history of atopic dermatitis occurring in the first year of life in Korean children. J Korean Med Sci. 2012;27: 723-8.
21. Kong HH, Oh J, Deming C, Conlan S, Grice EA, Beatson MA, et al. Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. Genome Res. 2012;22:850-9.
22. Rowlands D, Tofte SJ, Hanifin JM. Does food allergy cause atopic dermatitis? Food challenge testing to dissociate eczematous from immediate reactions. Dermatol Ther. 2006; 19:97-103.
23. Werfel T, Ballmer-Weber B, Eigenmann PA, Niggemann B, Rancé F, Turjanmaa K, Worm M. Eczematous reactions to food in atopic eczema: position paper of the EAACI and GA2LEN. Allergy. 2007;62:723-8.