

Risk factors of food sensitization in young children with atopic dermatitis

Araya Yuenyongviwat, Vanlaya Koosakulchai, Yada Treepaiboon, Wipa Jessadapakorn, Pasuree Sangsupawanich

Abstract

Background: Atopic dermatitis (AD) is a common chronic and relapsing skin disease in children and food allergies have been well documented in one-third of children. However, there are limit data about the risk factors of food sensitization in children with AD.

Objective: The aim of this study was to evaluate the risk factors associated with food sensitization, among AD children.

Methods: A cross-sectional study, from the electronic medical records of 119 AD patients, aged from 2 to 5 years were reviewed. The demographic data, onset and severity of AD, family history of atopy, age of first antibiotic usage, age of first applying and frequency of moisturizer used, age of introduction to allergenic foods and food specific IgE levels were recorded.

Results: The prevalence of food sensitization was; 60%. The most common food allergens were egg white (56.8%), cow's milk (40%) and wheat (34.7%). The significant factors associated with overall food sensitization were; history of parent-reported food allergies (OR = 4.4, $P = 0.001$), severe AD (OR = 4.5, $P = 0.03$) and breast feeding > 6 months (OR = 3.5, $P = 0.002$). Factors associated with egg white allergies were the history of parent-reported food allergies (OR = 3.8, $P = 0.02$), and severe AD (OR = 4.2, $P = 0.04$). There were also significant factors associated with cow's milk allergies this being; severe AD (OR = 6, $P = 0.03$) and a maternal history of asthma (OR = 10.9, $P = 0.01$).

Conclusions: Severe AD was a factor associated with all food sensitization, egg allergy and cow's milk allergy. Maternal asthma was also significantly associated with cow's milk allergy.

Key words: atopic dermatitis, food sensitization, children, risk factor, prevalence

From:

Department of Pediatrics, Faculty of Medicine,
Prince of Songkla University, Songkhla, Thailand

Corresponding author:

Araya Yuenyongviwat
Department of Pediatrics, Faculty of Medicine,
Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand
E-mail: taraya@medicine.psu.ac.th

Introduction

Atopic dermatitis (AD) is a common chronic and relapsing skin disease in children.^{1,2} The prevalence of AD is about; 10-30%, and 80% are affected before the age of 5.³ Children with AD experience itching along with on and off inflamed skin, which includes infected skin lesions, this in turn has an effect on their quality of life.^{4,5} The pathogenesis of AD are multifactorial factors, which included: mutation of the gene encoding fliaggrin (FLG) causing increased transepidermal water loss, and this is associated with the development of AD.⁶⁻⁸ Beside genetic factors, environment factors such as; microbes and allergens are also important in the development of skin inflammation.⁸⁻¹⁰

Food allergies (FA) have been well documented in approximately one-third of children, with moderate to severe AD, as a trigger of this inflammation.¹¹⁻¹³ Cow's milk, hen eggs, and peanuts are the most common allergens in young children.¹⁴ The evaluation of food sensitization in AD relies on measures of antigenic sensitization, such as; the skin prick tests and in vitro assays, that measure food specific immunoglobulin E (sIgE).¹⁵

There are previous studies, that have reported the associated between AD and food sensitization. Han et al. reported that rate of food sensitization was higher for all foods tested in the AD patients of those of less than 1 year of age, coupled

with moderate to severe AD.¹⁶ Mailhol et al. performed a cohort study from 386 AD patients. Their results showed that the prevalence of FA was 17.8%. Egg, peanuts, milk, tree nut and mustard accounted for 93% of cases.¹⁷ Wananukul et al. performed a retrospective cohort study in 205 AD patients, aged from; 2 months to 15 years. The results found 39% had food sensitization.¹⁸

However, there are limit data about the associated risk factor of food sensitization in pediatric AD patients. The aim of this study was to evaluate the prevalence along with risk factors associated with food sensitization among pediatric AD children.

Methods

The medical records of AD patients, aged from 2 months to 5 years, who attended the pediatric allergy clinic at tertiary referral center, from; January 2016 to December 2017 were reviewed, using ICD 10. The ICD 10 code were L 209: atopic dermatitis, unspecified and L 208: other atopic dermatitis. The diagnosis of AD was made using Hanifin and Rajka (Hanifin and Rajka, 1980) criteria by pediatric allergists. This study was approved by the Ethics Committee and Institutional Review Board. Consent was waived by the ethics committee, and the hospital gave permission to extract information from the database.

The data was collected from the medical records at initial visit, and demographic data included; sex, age, type of labor, underlying disease, onset of AD, severity of AD, family history of atopy (asthma, allergic rhinitis, atopic dermatitis and food allergy), age of first antibiotic usage, age of first applying and frequency of moisturizer used, and age of introduction to allergenic foods. The severity of AD was classified using the; Investigator Global Assessment Scale. Food specific IgE levels to cow's milk, egg white, egg yolk, soy, wheat, peanut, fish, and shrimp were recorded. Specific IgE for foods was conducted using Immucap. Sensitization to food was defined as; sIgE level ≥ 0.35 kUA/L. Cow's milk allergy, with an egg white being defined as; sIgE cow's milk or egg white $> 95\%$ PPV of food allergy (cow's milk sIgE ≥ 5 kUA/L for age ≤ 1 year of age,¹⁹ ≥ 15 kUA/L for age > 1 year of age²⁰ and egg white sIgE ≥ 0.35 kUA/L for age ≤ 2 years of age,²¹ ≥ 7 kUA/L for age > 2 years of age).²⁰

After extracting data from the medical records, the completed recorded form was used to interview parents via telephone calls.

Statistical analysis

The data were recorded using; Epidata, and analyzed was performed using; R statistical software. The demographic data were presented as; mean \pm standard deviation or median for continuous data, and number (%) for categorical data. Factors associated with food sensitization were analyzed using chi-square and Fisher's exact test. The strength of association was measured by odd's ratio (OR), with 95% confidence intervals (95%CI). A *P* value of less than 0.05 was regarded as significant.

Results

The medical records of 119 AD children were reviewed, with the median age being; 8 months (**Table 1**). Seventy-five children (63%) were male. Twenty-two children (18.5%) had a personal history of atopy, and parent-reported food allergies were the most common comorbidity. Common types of parent-reported food allergies were; egg yolk 25.9%, cow's milk 18.5%, wheat 18.5% and egg white 11.1%, with the symptoms of food allergy being; urticaria 66.7%, allergic proctocolitis 18.5%, angioedema 7.4% and anaphylaxis 7.4%. Median age of onset of AD was; 2 months, with the severity being (35.3%) mild, (50.4%) moderate and (14.3%) severe.

Table 1. Baseline characteristics

Characteristic	Total (N = 119)
Age (months), median (IQR)	8 (2, 69)
Sex, male, n (%)	75 (63.0)
Body weight (kg), mean (SD)	8.2 (2.8)
Body height (cm), mean (SD)	70 (11.2)
Mode of delivery, n (%)	
- Cesarean section	76 (64.0)
Personal history of atopy, n (%)	22 (18.0)
- Asthma	1 (0.8)
- Allergic rhinitis	3 (2.5)
- Parent-reported food allergy	20 (16.8)
Onset of rash (months), median (IQR)	2 (0.03, 36)
Severity of rash, n (%)	
- Mild	42 (35.3)
- Moderate	60 (50.4)
- Severe	17 (14.3)
Age of first antibiotic usage (months), median (IQR)	6 (0.03, 36)
Breast feeding, n (%)	114 (95.8)
Duration of breast feeding (months), median (IQR)	8 (1, 36)
Family history of atopy, n (%)	69 (57.9)
Maternal asthma, n (%)	5 (4.0)
Age of first applying moisturizer (months), median (IQR)	4 (0.03, 36)
Frequency of moisturizer used (day/week), mean (SD)	6.3 (1.5)
Age of introducing complementary food (months), mean (SD)	5.9 (0.6)

The prevalence of food sensitization was 60%, and the type of food allergens are shown in **Figure 1**. The most common food allergens were; egg white (56.8%) follow by cow's milk (40%) and wheat (34.7%).

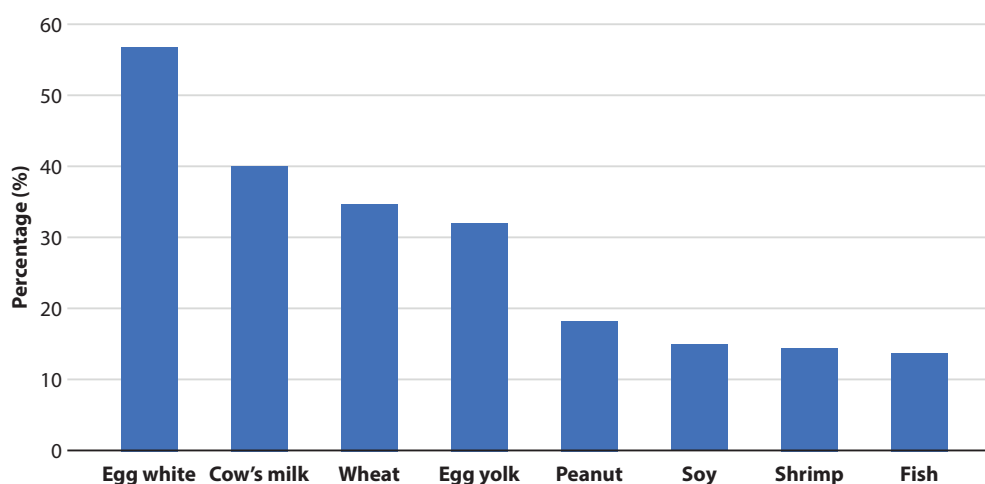


Figure 1. Prevalence of food sensitization in atopic dermatitis patients

Factors that might affect the development of food sensitization are shown in **Table 2**. Significantly factors associated with food sensitization were; a history of parent-reported food allergy ($P = 0.03$) and breast feeding > 6 months ($P = 0.004$). Age of introduction to allergenic foods was not found to be associated with food sensitization (data not shown).

Because; egg white and cow's milk were the most common food sensitization in this study, we also evaluated factors associated with egg white and cow's milk allergies, and the results are shown in **Table 3**. A significant factor that was associated

with an egg allergy were; history of a parent-reported food allergy ($P = 0.04$), whilst a factor being associated with a cow's milk allergy was; maternal asthma ($P = 0.01$). Age of introduction to egg white or cow's milk was not found to be associated with an egg white or cow's milk allergy.

The multivariate analysis of the factor associated with overall food sensitization, egg white and cow's milk allergies, are shown in **Table 4**. A significant association was found between; food sensitization and the history of parent-reported food allergies (OR = 4.4; 95%CI 1.2-15.9, $P = 0.001$).

Table 2. Risk factors associated with food sensitization in atopic dermatitis patients

Characteristic	No food sensitization (n = 47)	Food sensitization (n = 72)	P value
Sex, male, n (%)	30 (63.8)	45 (62.5)	1
Mode of delivery, n (%)			
- Cesarean section	28 (59.6)	48 (66.7)	0.55
Personal history of atopy, n (%)			
- Asthma	0 (0)	1 (1.4)	1
- Allergic rhinitis	1 (2)	2 (2.8)	0.47
- Parent-reported food allergy	3 (6.4)	17 (23.6)	0.03
Onset of rash (months), median (IQR)	2 (1, 4)	2 (1, 4)	0.13
Severity of rash, n (%)			0.06
- Mild	21 (45)	21 (29)	
- Moderate	23 (49)	37 (52)	
- Severe	3 (6)	14 (19)	
Age of first antibiotic usage (months), median (IQR)	4.5 (2, 8)	6 (3, 12)	0.15
Breast feeding > 6 months, n (%)	20 (42.5)	49 (68)	0.004
Maternal asthma, n (%)	1 (2.1)	4 (5.6)	0.64
Age of first applying moisturizer (months), median (IQR)	3 (2, 6)	4 (3, 7)	0.08
Frequency of moisturizer used (day/week), median (IQR)	7 (7, 7)	7 (7, 7)	0.23

Table 3. Risk factors associated with; egg white and cow's milk sIgE > 95% PPV of food allergy

	Egg white*			Cow's milk†		
	No (N = 45)	Yes (N = 50)	P value	No (N = 99)	Yes (N = 16)	P value
Sex, male, n (%)	17 (38)	16 (32)	0.70	61 (62)	12 (75)	0.45
Personal history of atopy, n (%)						
- Asthma	1 (2)	0 (0)	0.30	1 (1)	0 (0)	1
- Allergic rhinitis	2 (4)	0 (0)	0.07	1 (1)	0 (0)	1
- Parent-reported food allergy	4 (9)	14 (28)	0.04	15 (15)	3 (19)	0.71
Onset of rash (months), median (IQR)	2 (2, 2)	2 (2, 2)	0.44	2 (1, 4)	2 (1, 3)	0.98
Severity of rash, n (%)	0.13			0.06		
- Mild	18 (40)	13 (26)		38 (38)	3 (19)	
- Moderate	23 (51)	26 (32)		50 (51)	8 (50)	
- Severe	4 (9)	11 (22)		11 (11)	5 (31)	
Breast feeding > 6 months, n (%)	24 (53)	33 (66)	0.36	58 (59)	9 (56)	1
Family history of atopy, n (%)						
Paternal						
- Asthma	3 (6.7)	1 (2)	0.34	2 (2)	0 (0)	1
- Allergic rhinitis	14 (31)	12 (24)	0.58	27 (27)	4 (25)	1
- Atopic dermatitis	0 (0)	1 (2)	1	3 (3)	0 (0)	1
- Food allergy	3 (7)	0 (0)	0.10	3 (3)	1 (6)	0.45
Maternal						
- Asthma	2 (4.4)	3 (6)	1	2 (2)	3 (19)	0.01
- Allergic rhinitis	12 (26)	11 (22)	0.77	25 (25)	5 (31)	0.75
- Atopic dermatitis	2 (4.4)	3 (6)	1	5 (5)	1 (6)	1
- Food allergy	2 (4.4)	1 (2)	0.60	4 (4)	1 (6)	0.53
Sibling						
- Asthma	6 (13)	2 (4)	0.12	11 (11)	1 (6)	0.67
- Allergic rhinitis	6 (13)	2 (4)	0.12	8 (8)	0 (0)	0.33
- Atopic dermatitis	5 (11)	3 (6)	0.45	11 (11)	0 (0)	0.18
- Food allergy	4 (9)	1 (2)	0.17	7 (7)	1 (6)	1
Age of first applying moisturizer (months), median (IQR)	3 (2, 6)	4 (3, 6)	1	4 (2, 6)	4.5 (3, 6)	0.69
Age of introduction to cow's milk (months), median (IQR)	7 (0.03, 14)	2 (0.03, 12)	0.27	2 (0.03, 12)	1 (0.03, 3)	0.20
Age of introduction to egg white (months), median (IQR)	9 (7, 12)	12 (7, 12)	0.19	10 (7, 12)	12 (8, 12)	0.94

* Egg white sIgE > 95% PPV of food allergy are > 0.35 kUA/L for ages < 2 years old and > 7 kUA/L for ages > 2 years old.

† Cow's milk sIgE > 95% PPV of food allergy are > 5 kUA/L for ages < 1 year old and > 15 kUA/L for ages > 1 year old.

Table 4. Multivariate logistic analysis of factors associated with food sensitization, egg white and cow's milk sIgE > 95% PPV of a food allergy in atopic dermatitis patients

	Overall food sensitization		Egg white sIgE > 95% PPV of food allergy [†]		Cow's milk sIgE > 95% PPV of food allergy [‡]	
	ORa* (95%CI)	P value	ORa* (95%CI)	P value	ORa* (95%CI)	P value
Parent-reported food allergy	4.4 (1.2-15.9)	0.01	3.8 (1.1-12.7)	0.02	1.2 (0.3-4.8)	0.80
Severity of rash						
- Mild	1		1		1	
- Moderate	1.7 (0.7-3.8)	0.20	1.78 (0.7-4.6)	0.23	2.2 (0.5-8.8)	0.28
- Severe	4.5 (1.1-18.0)	0.03	4.2 (1.06-16.5)	0.04	6 (1.2-29.0)	0.03
Breast feeding > 6 months	3.5 (1.5-7.4)	0.002	1.6 (0.7-3.8)	0.29	0.9 (0.3-2.8)	0.87
Maternal asthma	2.9 (0.3-27.2)	0.30	1.39 (0.2-8.8)	0.73	10.9 (1.6-73)	0.01

* adjusted odds ratio by sex, age

[†] Egg white sIgE > 95% PPV of food allergy are > 0.35 kUA/L for ages < 2 years old and > 7 kUA/L for ages > 2 years old.

[‡] Cow's milk sIgE > 95% PPV of food allergy are > 5 kUA/L for ages < 1 year old and > 15 kUA/L for ages > 1 year old.

Severe AD was significantly associated with food sensitization (OR = 4.5; 95% CI 1.1-18, $P = 0.03$). Breast feeding > 6 months was also significantly associated with food sensitization (OR = 3.5; 95%CI 1.5-7.4, $P = 0.002$).

In addition, a significant association was found between an egg white allergy, and the history of parent-reported food allergies (OR = 3.8; 95%CI 1.1-12.7, $P = 0.02$). Severe AD was significant associated with an egg white allergy (OR = 4.2; 95%CI 1.06-16.5, $P = 0.04$) as well as a cow's milk allergy (OR = 6; 95%CI 1.2-29, $P = 0.03$). Maternal asthma was also significantly associated with a cow's milk allergy (OR = 10.9; 95%CI 1.6-73, $P = 0.01$).

Discussion

This study, from 119 children with AD, shows a prevalence of overall food sensitization at; 60%. The most common food allergens were; egg white (56.8%), cow's milk (40%), wheat (34.7%). While previous studies found that; 30-40% of AD patients had food sensitization, with the common food allergens being; egg white, wheat, cow's milk and egg yolk.^{18,22} Whereas, our study found a higher prevalence of food sensitization than these studies. This may be explained by the general prevalence of food allergies being higher in young children, whereas the previous study had enrolled patients until 15 years of age, but our study enrolled patients younger than 6 years of age. Contrary, when comparing between; our study, and the study of Han et al., that enrolled patients at 4 years of age, the prevalence of food sensitization was also high (51%).¹⁶ Egg white, cow's milk and wheat were the most common food allergen in our study.

Authors' study found that risk factors associated with overall food sensitization and an egg white allergy were; a history of parent-reported food allergy, severe AD and breast feeding of more than 6 months. In addition, maternal history of asthma was also significantly associated with a cow's milk allergy. Previous studies have shown that a young age, ≤ 2 years, and the onset of AD before 3 months of age is associated with

food sensitization.¹⁶⁻¹⁷ However, in our study, we did not find any significant association between; a young age and food sensitization, in addition, early onset of AD was not found to be a risk factor of food sensitization in our study. Our study also showed that severe AD was a factor associated, with food sensitization and food allergies, as with previous studies.¹⁶⁻¹⁷

A family history of atopy was a risk factor for the development of food allergy in several studies. Koplin et al performed a population-based study, the results showed association between family history of atopy and food allergy (OR = 1.4, 95%CI 1.1-1.7).²³ Celakovska et al performed a cohort study, the results showed associated between family history of atopy and food allergy in atopic dermatitis patients.²⁴ Our study found that maternal asthma was significantly associated with a cow's milk allergy.

Furthermore, our study found that breast feeding of more than 6 months was also associated with food sensitization, as well as an egg white allergy. This might possibly be explained by the parents of children, who are prone to developing food sensitization, or food allergies, were concerned, and had the intention to breast feed longer than the normal population. However, we did not find an association between; age of first applying moisturizer, or the age of introduction to allergenic foods, and food sensitization.

There were several limitations associated to this study such as; the severity of AD in this study was found using an IGA scale, which is less detailed than the SCORAD index, however in general practice it is easier to perform, and less time consuming. Our study used sIgE only, for diagnosis of a food allergy, and was not confirmed by the; oral food challenge test. However, we were using a cut point of; 95% positive predictive value of sIgE for diagnosis of a food allergy, which is in line with the same practice in general situations. Additionally, our study might have recall bias due to after extracting data from medical records, the completed recorded form was used to interview parents via telephone conversations.

Conclusion

The prevalence of food sensitization in AD children is high. The most common food allergens were egg white, cow's milk and wheat. Severe AD was a significant factor associated with all food sensitization, egg allergy and cow's milk allergies. Maternal asthma was also significantly associated with cow's milk allergy.

Conflict of interest

The authors declare that they have no competing interests.

Author contributions

- AY designed the study and performed the analysis and manuscript preparation
- VK, collected data, designed the study and performed the data analysis
- YT, WJ collected data
- PS designed the study, performed the data analysis and reviewed the manuscript.
- All authors have read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee and Institutional Review Board. Consent was waived by the ethics committee. The hospital gave permission to extract information from the database.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated during the current study are available from the corresponding author upon reasonable request.

References

1. Bieber T. Atopic dermatitis. *Ann Dermatol.* 2010;22:125-37.
2. Boguniewicz M, Fonacier L, Guttman-Yassky E, Ong PY, Silverberg J, Farrar JR. Atopic dermatitis yardstick: Practical recommendations for an evolving therapeutic landscape. *Ann Allergy Asthma Immunol.* 2018;120(1):10-22.e2.
3. Levy RM, Gelfand JM, Yan AC. The epidemiology of atopic dermatitis. *Clin Dermatol.* 2003;21:109-15.
4. Krakowski AC, Eichenfield LF, Dohil MA. Management of atopic dermatitis in the pediatric population. *Pediatrics.* 2008;122:812-24.
5. Chamlin SL, Frieden IJ, Williams ML, Chren MM. Effects of atopic dermatitis on young American children and their families. *Pediatrics.* 2004;114:607-11.
6. Leung DY, Boguniewicz M, Howell MD, Nomura I, Hamid QA. New insights into atopic dermatitis. *J Clin Invest.* 2004;113:651-7.
7. Rodriguez E, Baurecht H, Herberich E, Wagenpfeil S, Brown SJ, Cordell HJ, et al. Meta-analysis of flaggirin polymorphisms in eczema and asthma: robust risk factors in atopic disease. *J Allergy Clin Immunol.* 2009;123:1361-70.
8. Leung DYM, Berdyshev E, Goleva E. Cutaneous barrier dysfunction in allergic diseases. *J Allergy Clin Immunol.* 2020;145(6):1485-97.
9. Kubo A, Nagao K, Amagai M. Epidermal barrier dysfunction and cutaneous sensitization in atopic diseases. *J Clin Invest.* 2012;122:440-7.
10. Bieber T. Atopic dermatitis. *N Engl J Med.* 2008;358:1483-94.
11. Breuer K, Heratizadeh A, Wulf A, Baumann U, Constien A, Tetau D, et al. Late eczematous reactions to food in children with atopic dermatitis. *Clin Exp Allergy.* 2004;34:817-24.
12. Sampson HA. Role of immediate food hypersensitivity in the pathogenesis of atopic dermatitis. *J Allergy Clin Immunol.* 1983;71:473-80.
13. Eigenmann PA, Sicherer SH, Borkowski TA, Cohen BA, Sampson HA. Prevalence of IgE-mediated food allergy among children with atopic dermatitis. *Pediatrics.* 1998;101:E8.
14. Burks AW, Mallory SB, Williams LW, Shirrell MA. Atopic dermatitis: clinical relevance of food hypersensitivity reactions. *J Pediatr.* 1988;113:447-51.
15. Hanifin JM, Ragka G. Diagnostic feature of atopic dermatitis. *Acta Derm Venereol.* 1980;92:S44-7.
16. Han DK, Kim MK, Yoo JE, Choi SY, Kwon BC, Sohn MH, et al. Food sensitization in infants and young children with atopic dermatitis. *Yonsei Med J.* 2004;45:803-9.
17. Mailhol C, Giordano-Labadie F, Lauwers-Cances V, Ammouy A, Paul C, Rance F. Point prevalence and risk factors for food allergy in a cohort of 386 children with atopic dermatitis attending a multidisciplinary dermatology/paediatric allergy clinic. *Eur J Dermatol.* 2014;24:63-9.
18. Wananukul S, Chatproedprai S, Tempark T, Phuthongkamt W, Chatchatee P. The natural course of childhood atopic dermatitis: a retrospective cohort study. *Asian Pac J Allergy Immunol.* 2015;33:161-8.
19. García-Ara C, Boyano-Martínez T, Díaz-Pena JM, Martín-Muñoz F, Reche-Frutos M, Martín-Esteban M. Specific IgE levels in the diagnosis of immediate hypersensitivity to cows' milk protein in the infant. *J Allergy Clin Immunol.* 2001;107(1):185-90.
20. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol.* 2001;107(5):891-6.
21. Boyano-Martínez T, García-Ara C, Díaz-Pena JM, Martín-Esteban M. Prediction of tolerance on the basis of quantification of egg white-specific IgE antibodies in children with egg allergy. *J Allergy Clin Immunol.* 2002;110(2):304-9.
22. Somanunt S, Chinratanapisit S, Pacharn P, Visitsunthorn N, Jirapongsananuruk O. The natural history of atopic dermatitis and its association with Atopic March. *Asian Pac J Allergy Immunol.* 2017;35:137-143.
23. Koplin JJ, Allen KJ, Gurrin LC, Peters RL, Lowe AJ, Tang ML, et al. The impact of family history of allergy on risk of food allergy: a population-based study of infants. *Int J Environ Res Public Health.* 2013;10:5364-77.
24. Celakovska J, Bukac J. Analysis of food allergy in atopic dermatitis patients - association with concomitant allergic diseases. *Indian J Dermatol.* 2014;59:445-50.