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The natural history of atopic dermatitis and its association with Atopic March

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Abstract

Background: Atopic dermatitis (AD) is the first manifestation of Atopic March. The natural history of AD and predictive factors for Atopic March have not been widely studied in Asia.

Objective: To study the natural history and associated factors of disease remission and risk of respiratory allergy in Thai children with AD.

Method: Medical records of AD patients attending Allergy clinic at Siriraj hospital from 2004-2014 were reviewed. Patients were further followed-up to obtain current symptoms and treatment.

Results: One hundred and two AD patients (60.8% female) were followed for 10.2±4.7 years. The median age at diagnosis was 1.5 (0.1-12.0) years. The most common allergen sensitization was *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*. Forty-four percent of patients had complete remission at the median age of 6.3 (2.0-15.0) years. Forty-seven percent of early AD patients (onset <2 years) had concomitant food allergy which egg and cow's milk were leading causes. The remission rate of AD was higher in early AD than later onset AD (p=0.02). Allergic rhinitis (AR) and asthma were diagnosed in 61.8% and 29.4% of the patients at the median age of 4.6 and 3.8 years, respectively. Early AD and food allergies were significantly associated with early asthma (onset <3years) (OR=10.80, p<0.01 and OR=8.70, p=0.01).

Conclusions: Almost half of AD children had complete remission at school age with a better prognosis in early AD. At preschool age, two-thirds and one-third developed AR and asthma, respectively. Early AD and food allergy were risk factors of early asthma.

Keywords: allergic rhinitis, asthma, atopic dermatitis, Atopic March, children, food allergy, natural history

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Introduction

Atopic dermatitis (AD) is a common chronic allergic skin disease in children. It can present in early infancy or later.[1] An increased prevalence of AD, allergic rhinitis (AR) and asthma was reported.[2-5] The mechanism of AD could be partly explained by defective genes, skin barriers and allergen triggers.[1,6,7] *Filaggrin* gene mutation was proposed as a risk factor for AD, asthma, AR and peanut allergy.[8] Most AD patient had an onset of disease before 5 years of age.[8] Atopic March is the progression of atopic diseases. Patients with AD in infancy increase the risk of food allergy and respiratory allergy (AR and asthma) in late childhood.[9,10] Sensitization to cat and house dust mites was reported to increase the risk of asthma in AD patients.[11]

The natural course of AD and its association with respiratory allergy were studied in many countries. In Germany, the natural course of AD from birth to 7 years of age was investigated.[12] Forty percent of early AD (onset before 2 years of age) had complete remission at 3 years of age. The severity of AD was the strongest risk of persistent disease and early AD was associated with asthma at school age. Positive specific IgE (sIgE) to food was found in early AD, and aeroallergen sensitization increased when patients grew up.[12]

In Asia, Korean AD patients developed disease in the first year of life, were followed for 5.8 years. The maternal diet restriction during breast feeding and negative sensitization

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to cow's milk were associated with disease remission in moderate-severe AD.[13] In Taiwan, a prospective birth cohort study from prenatal until 6 years of age, reported that most patients who had AD before 6 month of age, had remission within 6 years.[14] Factors associated with persistent disease were egg-white sensitization and more than 2 areas of AD lesions at 6 months of age. This group of patients had increased risk of asthma at the age of 6 years.[14] In Singapore, children with family history of atopic disease were followed from antenatal until 5 years of age. Twenty-seven percent had eczema in the first two years of life (early eczema), which decreased to 11.9% at 5 years of age. Early wheeze (onset less than 2 years of age) with or without house dust mite sensitization increased the risk of wheeze at 5 years. Early onset eczema and house dust mite sensitization at the age of 2 years increased the risk of AR at the age of 5 years.[15] In Thailand, a recent report of AD followed by pediatric dermatologists showed that early onset (less than 2 year of age) and severity of AD determined the prognosis of disease during the 5-year observation period. The late onset of AD was associated with AR while family history of atopy was associated with asthma.[16]

AD is a chronic relapsing disease. The long follow-up period may provide a better picture of the natural course of the disease and the development of Atopic March. Understanding the natural history and risk factor of disease progression will help physicians to manage AD patients and monitor atopic diseases in high risk group. The purpose of this study was to evaluate the natural history of AD, and the associated factors with disease remission and the risk of Atopic March in children with AD from the allergist's perspective, during the 10-year observation period.

Methods

Study design

Medical records of AD patients who attended the pediatric allergy clinic at Siriraj hospital from 2004 to 2014 were reviewed using ICD 10. The ICD 10 codes were L 20.9: atopic dermatitis, unspecified and L 20.8: other atopic dermatitis. The diagnosis was made using Hanifin and Rajka criteria by pediatric allergists.[17] Progression of AD and Atopic March were recorded upon follow-up or telephone interview. AD patients who completed follow up or telephone interview for their current status were included in this study. Patients who had chronic diseases such as cardiac, endocrine, neurologic, liver or renal diseases were excluded. The study was approved by the Siriraj Institutional Review Board (715/2557(EC4). The clinical trial number was NCT02532920. Inform consent/assent was obtained by patients and parents.

The demographic data included personal data, onset of AD, family history of atopy (AD, food allergy, AR and asthma), environmental exposure (pet, smoking), skin prick test (SPT)/ sIgE to food/ aeroallergen, symptom and treatment at each visit. The severity of AD was classified using Scoring Atopic Dermatitis (SCORAD): mild (<25), moderate (>25-49), severe (>50) depended on area, intensity and subjective symptoms.[17] The natural history of AD was categorized into 3 groups as follows: complete remission (no clinical of AD for at least one year without using topical steroid/ calcineurin inhibitor), persistent (had clinical of AD and need topical steroid/ calcineurin inhibitor at least once a month) and intermittent (other than above).[13] Asthma, AR and food allergies were diagnosed by pediatric allergists. AD with an onset less than 2 years of age was defined as early AD. Asthma at the onset less than 3 years of age was defined as early asthma.[18]

Patients were followed periodically and symptoms, SPT or sIgE and treatments were recorded. Patients who were lost to follow-up or could not come to the hospital were interviewed by telephone and the current status and treatment were recorded. They were invited to visit the pediatric allergy clinic if they had uncontrolled AD or developed respiratory allergy or needed to be evaluated for allergic sensitization.

SPT was done using standard commercial allergen from ALK-Abello (Port Washington, NY, USA). The Bermuda and Johnson grass, acacia, careless weed, *Alternaria tenuis*, *Cladosporium Sphaerospermur*, *Curvularia inaequalis*, American cockroach, German cockroach, mite ((*Dermatophagoides pteronyssinus (Dp)*, *Dermatophagoides farinae (Df)*), egg-white, egg-yolk, cow's milk, and soy and wheat grain, were used. Histamine phosphate (10 mg/ml) and glycerinated saline were used as positive and negative controls, respectively. A positive result was defined as a wheal diameter greater than 3 mm compared to the negative control. Specific IgE for food and aeroallergen were done using Immunocap (Port Washington, NY, USA). Positive results were defined as level ≥ 0.35 KUA/L.

Statistical analysis

The demographic data were presented by mean ± standard deviation or median (range) for continuous data and number (%) for categorical data. Factors associated with early AD and Atopic March were analyzed using chi-square and Fisher's exact test. The strength of association was measured by odds ratio (OR) and 95% confidence intervals (95% CI). Kaplan -Meier curve and log rank test were used to evaluate the effect of AD onset and time to remission. Multivariate Cox proportional hazards regression model, hazard ratio (HR) and 95% CI were analyzed and adjusted for confounding factors. Results were considered statistically significant at a p-value < 0.05. All statistical analysis was performed using PASW Statistics (SPSS) 18.0 (SPSS Inc., Chicago, IL., USA).

Results

Demographic data

The medical records of 102 AD children were reviewed. Sixty percent of patients were female. The follow-up period was 10.2 ± 4.7 years. The median age of AD onset was 1.5 (range 0.08-12.0) years with the AD severity being mild (79.4%), moderate (13.7%) and severe (6.9%). The early AD was found in 55.9% of total subjects. Forty-four percent of patients had complete remission at the median age of 6.3 (range 2.0-15.0) years. The family history of atopy (AD, AR, asthma and food allergy) was reported in 55% of patients. Environmental exposure such as smoke and pets (cat, dog) were reported in 45% of patients. Food allergy was found in 30% of patients, with the elicited foods being egg 9.8%, cow's milk 6.9%, seafood 4.9% and wheat 3.9%. Respiratory allergy was reported in 91.2% of patients and 61.8% and 29.4% of them had the diagnosis of AR and asthma, respectively.

Table 1. Factors associated with early onset atopic dermatitis

	AD onset < 2 years (n=57) n (%)	AD onset ≥ 2 years (n=45) n (%)	*P* value	Odd ratio (95% CI)
Severity			**0.03**	
Mild	44 (77.2)	37 (82.2)		
Moderate	6 (10.5)	8 (17.8)		
Severe	7 (12.3)	0 (0)		
Skin distribution				
Head (n=15)	11 (19.3)	4 (9.3)	0.26	2.33 (0.68-7.9)
Face (n=37)	32 (56.1)	5 (11.6)	**<0.01**	**9.70 (3.34-28.5)**
Chest (n=17)	14 (24.6)	3 (7.0)	**0.03**	**4.34 (1.10-16.1)**
Back (n=23)	15 (26.3)	8 (18.6)	0.47	1.56 (0.63-4.11)
Leg (n=72)	37 (64.9)	35 (81.4)	0.08	0.42 (0.16-1.08)
Arm: flexor area (n=74)	37 (64.9)	37(86.0)	**0.02**	**0.30 (0.10-0.83)**
Food allergy (n=31)	27 (47.4)	4 (8.9)	**<0.01**	**9.20 (2.90-29.4)**
Cow's milk (n=13)	11 (19.3)	2 (4.4)	**0.03**	**5.12 (1.07-2.43)**
Egg (n=16)	15 (26.3)	1 (2.2)	**<0.01**	**1.56 (1.98-125)**
Wheat (n=6)	5 (8.8)	1 (2.2)	0.26	4.23 (0.467-37)
Allergen sensitization (SPT) at age < 2 years				
Indoor allergen (cat, dog, HDM, Am Cr, Ger Cr) (n=4)	3 (75)	0 (0)	0.40	2.0 (0.52-8.0)
EW, EY, CM, soy (n=14)	3 (21.4)	1 (50)	0.45	0.27 (0.01-5.78)
Family history of atopy (n=57)	30 (52.6)	27 (60)	0.55	0.74 (0.33-1.63)
Environment				
Pets (cat, dog) (n=27)	18 (31.6)	9 (20.0)	0.19	1.84 (0.76-4.62)
Smoking (n=19)	11 (19.3)	8 (17.8)	0.85	1.11 (0.40-3.03)
Diet				
Maternal diet during pregnancy (avoid egg, CM, soy) (n=9)	6 (10.5)	3 (6.7)	0.50	1.66 (0.40-6.99)
Maternal diet during breast feeding (avoid egg, CM, soy) (n=8)	4 (7)	4 (8.9)	0.73	0.77 (0.18-3.27)
Exclusive breast feeding 6 month (n=25)	14 (26.4)	11 (44)	0.99	1.0 (0.40-2.50)
Start semisolid > 6 month (n=63)	31 (54.4)	32 (71.1)	0.08	0.50 (0.21-1.11)

AD, atopic dermatitis; Am Cr, American cockroach; CM, cow's milk; EW, egg white; EY, egg yolk; Ger Cr, German cockroach; HDM: house dust mite

Treatment of AD depended on severity of the disease. Skin hydration and allergen avoidance were done in all groups. In severe AD, all patients were instructed to use a wet wrap on exacerbation. Topical steroid, topical antibiotic, topical calcineurin inhibitor and oral antibiotics were mostly used in severe cases. Subcutaneous immunotherapy (SCIT) was performed in 8 patients. Eighty-seven percent of SCIT cases had moderate severity. All of them had respiratory allergy, and 62.5% and 37.5% had the diagnosis of AR and asthma, respectively.

***Factors associated with early AD* (Table 1)**

Children with early AD had higher severity than those who developed AD at or after 2 years of age (p=0.03). The skin lesion on face and chest was found in early AD more than later onset AD (OR=9.70, 95% CI; 3.34-28.50, p<0.01 and OR=4.34, 95% CI; 1.10-16.10, p=0.03, respectively). In contrast, skin lesion at arms (flexor area) was found in early AD less than later onset AD (OR=0.30, 95% CI; 0.10-0.38, p=0.02). All food allergies were more frequently found in early AD (OR=9.20, 95% CI; 2.90-29.40, p<0.01) as were egg (OR=1.56, 95% CI; 1.98-125, p<0.01) and cow's milk allergies (OR=5.12, 95% CI; 1.07-2.43, p=0.03). Allergen sensitization prior to 2 years of age, family history of atopy, environmental exposure and dietary history were not related to the onset of AD.

Food and aeroallergen sensitization

Seventy-nine SPT and 39 sIgE were performed overtime to evaluate aeroallergen and food sensitization. The positive result of SPT was shown in **Figure 1**. The common sensitized food which was egg-white, egg-yolk, cow's milk and soy were shown in **Figure 1A**. There was a trend that the food sensitization rate was highest at ages below 2 years. The aeroallergen sensitization is shown in **Figure 1B**. The most common aeroallergen sensitization in all age groups was *Dp*, followed by *Df*. The highest *Dp* and *Df* sensitizations were found in the older than 7 years group. There was a trend that aeroallergen sensitization was increased when the patients grew older.

The sIgE to food was tested in patients who were unable to obtain SPT. Food sensitization by sIgE was also highest at ages below 2 years. At that age, positive sIgE was 73% for egg-white, 66% for egg-yolk and 62% for cow's milk.

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Table 2. Variables associated with the natural history of atopic dermatitis

		Complete remission (n=45)	Persistent/ intermittent (n=57)	*P* value
Age of onset				**0.02**
	< 2 years n=57, n (%)	28 (49.1)	29 (50.9)	
	≥ 2 years n=45, n (%)	17 (37.8)	28 (62.2)	
Severity at onset				0.13
	Mild n=81, n (%)	38 (46.9)	43 (51.1)	
	Moderate n=14, n (%)	4 (28.6)	10 (71.4)	
	Severe n=7, n (%)	3 (42.9)	4 (57.1)	
Food allergy n=31, n (%)		14 (45.2)	17 (54.8)	0.34
Atopic disease	Asthma n=30, n (%)	17 (56.7)	13 (43.3)	0.13
	Allergic rhinitis n=63, n (%)	25 (39.7)	38 (60.3)	0.14
Family history atopy n=57, n (%)		30 (52.6)	27 (47.4)	0.12
Environment	Pets (dog, cat) n=27, n (%)	14 (51.9)	13 (48.1)	0.25
	Smoking n=19, n (%)	11 (57.9)	8 (42.1)	0.50
Diet				
Maternal diet during pregnancy (avoid egg, CM, soy) n=9, n (%)		3 (33.3)	6 (66.7)	0.93
Maternal diet during breast feeding (avoid egg, CM, soy) n=8, n (%)		2 (25.0)	6 (75.0)	0.53
Exclusive breast feeding for 6 month n=25, n (%)		11 (44.0)	14 (56.0)	0.73
Start semisolid > 6 month n=63, n (%)		29 (46.0)	34 (54.0)	0.13

CM, cow's milk.

Variables associated with AD remission

The median age of AD remission was 6.3 (range 2.0-15.0) years. The median age of onset of AD in complete remission and the persistent/intermittent group was 1.16 years (0.08-12.0) and 1.5 years (0.08-10.0), respectively. In early AD, almost 50% had complete remission at the median age of 4.3 (2.0-15.0) years. **Table 2** and **Figure 2** showed that patients with early AD had higher remission rates than patients with late onset AD (Kaplan-Meier survival analysis, p=0.02). After adjusting for AD severity and family history of atopy, early AD had a higher rate of remission than later onset AD (hazard ratio = 2.35 (95% CI: 1.25-4.44, p<0.01).

Figure 1.

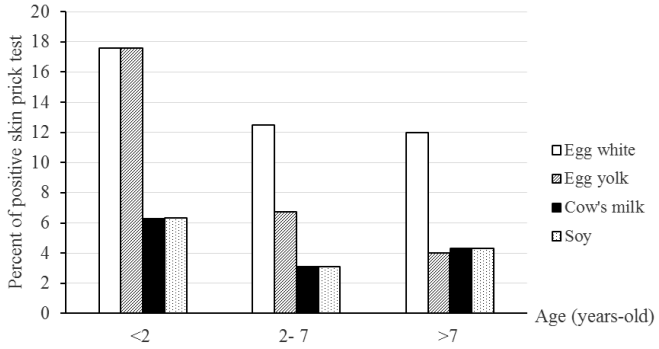

Figure 1A. Positive skin prick test to food allergens in 3 different age groups

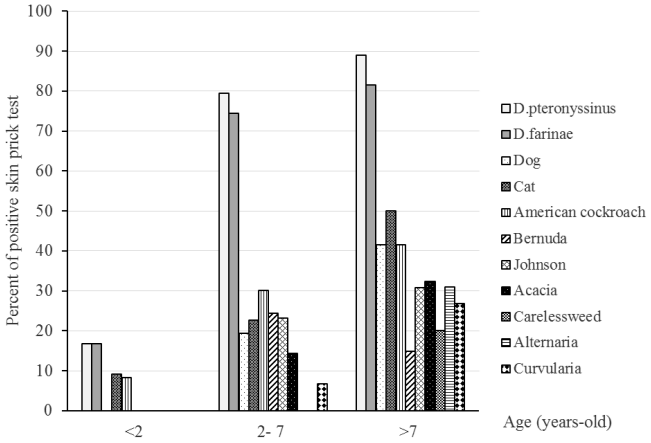

Figure 1B. Positive skin prick test to aeroallergens in 3 different age groups

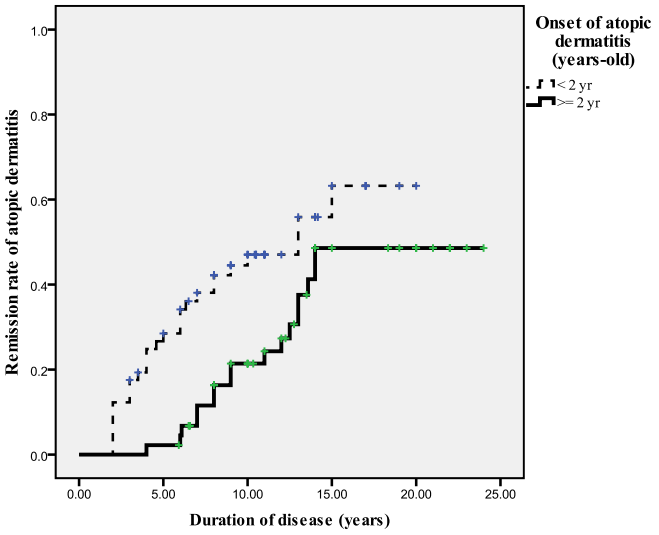

Figure 2. Kaplan-Meier survival analysis of remission rate of AD in early AD and later onset AD patients. Patients with early AD had higher remission rate than patients with later onset AD (p=0.02).

Table 3. Factors associated with atopic march

		AR (n=63) n (%)	No AR (n=39) n (%)	*P* value	Asthma (n=30) n (%)	No asthma (n=72) n (%)	*P* value	Asthma onset < 3 years (n= 13) n (%)	Asthma onset ≥ 3 years (n=17) n (%)	*P* value
Onset of AD	<2 years	28 (44.4)	29 (74.4)	**<0.01**	17 (56.7)	40 (55.6)	0.92	11 (84.6)	6 (35.3)	**<0.01**
	≥2 years	35 (55.6)	10 (25.6)	**<0.01**	13 (43.3)	32 (44.4)	0.92	2 (15.4)	11 (64.7)	**<0.01**
Severity of AD at onset	Mild	52 (82.5)	29 (74.4)	0.29	25 (83.3)	56 (77.8)	0.65	12 (93.2)	13 (76.5)	0.11
	Moderate	6 (9.5)	8 (20.5)	0.29	4 (13.3)	10 (13.9)	0.65	0 (0)	4 (23.5)	0.11
	Severe	5 (7.9)	2 (5.1)	0.29	1 (3.3)	6 (8.3)	0.61	1 (7.7)	0 (0)	0.11
Food allergy		15 (23.8)	23 (59.0)	0.07	9 (30)	22 (30.6)	0.96	7 (53.8)	2 (11.8)	**0.01**
Allergen sensitization (SPT) at age < 2 years										
Indoor allergens (cat, dog, HDM, Am Cr, Ger Cr) (n/ positive test, (%))		0	3/3 (100.0)	0.1	1/3 (33.3)	2/3 (66.7)	1	1/1 (100.0)	0	1
Food (EW, EY, CM, soy) (n/ positive test, (%))		1/4 (25.0)	3/4 (75.0)	1	1/4 (25.0)	3/4 (75.0)	1	1/1 (100.0)	0	1
Allergen sensitization (SPT) at age 2-7 years										
Indoor allergens (cat, dog, HDM, Am Cr, Ger Cr) (n/ positive test, (%))		20/27 (74.1)	7/27 (25.9)	0.49	10/27 (37.0)	17/27 (63.0)	0.53	4/10 (40.0)	6/10 (60.0)	1
Food (EW, EY, CM, soy) (n/ positive test, (%))		4/5 (80.0)	1/5 (20.0)	1	1/5 (20.0)	4/5 (80.0)	0.63	1/1 (100.0)	0	1
Allergen sensitization (SPT) at age > 7 years										
Indoor allergens (cat, dog, HDM, Am Cr, Ger Cr) (n/ positive test, (%))		25/32 (78.1)	7/32 (21.9)	0.64	10/32 (31.3)	22/32 (68.8)	1	2/10 (20.0)	8/10 (80.0)	1
Food (EW, EY, CM, so (n/ positive test, (%))		2/3 (66.7)	1/3 (33.3)	1	0	3/3 (100)	1	0	0	1
Family history of atopy		35 (55.6)	22 (56.4)	0.93	21 (70)	36 (50)	0.06	9 (69.2)	12 (70.6)	0.94
Environment	Pets (cat, dog)	15 (23.8)	12 (30.8)	0.44	11 (36.7)	16 (22.2)	0.13	7 (53.8)	4 (23.5)	0.09
	Smoking	12 (19.0)	7 (17.9)	0.89	7 (23.3)	12 (16.7)	0.41	3 (23.1)	4 (23.2)	0.98
Diet										0.47
Maternal diet during pregnancy (avoid egg, CM, soy)		2 (3.2)	7 (17.9)	0.01	1 (3.3)	8 (11.1)	0.21	1 (7.7)	0 (0)	0.43
Maternal diet during breast feeding (avoid egg, CM, soy)		3 (4.8)	5 (12.8)	0.14	1 (3.3)	1 (9.7)	0.27	1 (7.7)	0 (0)	0.43
Exclusive breast feeding for 6 month		17 (27)	8 (20.5)	0.46	7 (23.3)	18 (2)	0.86	2 (15.4)	5 (29.4)	0.42
Start semisolid > 6 month		39 (61.9)	24 (61.5)	0.97	21 (70)	42 (58.3)	0.27	10 (76.9)	11 (64.7)	0.47

AD, atopic dermatitis; Am Cr, American cockroach; AR, allergic rhinitis; CM, cow's milk; EW, egg white; EY, egg yolk; Ger Cr, German cockroach; HDM: house dust mite.

Variables which might be associated with the course of AD were shown in **Table 2**. The severity of AD, food allergy, other atopic diseases, family history of atopy, environmental exposure and dietary history, were not associated with the remission of AD.

The development of Atopic March

Allergic rhinitis and asthma were diagnosed in 61.8% and 29.4% of the patients at the median age of 4.6 (1.0-12.0) years and 3.8 (1.25-8.0) years, respectively. Sixty-seven percent of asthmatic patients also had AR. Factors that might affect the development of AR and asthma were shown in **Table 3**. The development of AR was lower in early AD (44.4%) than later onset AD patients (55.6%) (OR=0.28, 95% CI 0.11-0.66, p<0.01). Maternal dietary avoidance during pregnancy (avoid egg, cow milk and soy) decreased the risk of AR (OR=0.15, 95% CI 0.03-0.76, p=0.01). The development of early asthma was more in early AD (84.6%) than later onset AD patients (15.4%) (OR=10.08, 95% CI; 1.66-61.33, p<0.01) as well as patients with food allergy (OR=8.7, 95% CI; 1.39-55.56, p<0.01). The severity of AD, family history of atopy, environmental exposure and allergen sensitization were not associated with the development of AR or asthma.

Discussion

Atopic dermatitis is a chronic relapsing skin condition. Understanding the natural course and development of Atopic March required long-term follow-up. Our study is a retrospective cohort with 10-year-observation time. It was considered longer than studies from Germany, Korea, Taiwan and the recent report from Thailand (7 years, 5 years, 6 years, and 5.2 years, respectively).[12-14,16]

Previous studies showed that the early AD had higher rate of food allergy than later onset AD patients.[19,20] Our study supported a trend that food sensitization rate was higher at ages below 2 years than in older children. In contrast, there was a trend that aeroallergen sensitization rate was higher at school age than younger ages. This supported the concept of Atopic March, as food allergen sensitization decreased when patients grew older, while aeroallergen sensitization increased.[11,21] The most common aeroallergen was house dust mite, which is the most important aeroallergen in Thailand.[5] It could be a trigger of AD and prolong the natural course of this disease. Our study found lower food allergy in AD children than previous studies.[19,22] It was possibly explained by the majority of cases being mild AD in our study, while in other studies they were moderate to severe AD.

The natural course of AD in this study was categorized into complete remission, persistent or intermittent, according to the study by Chung *et al.*[13] We used this category since it combined both clinical and treatment to classify the course of AD. In Asia, the remission rate of AD was 70% in Korean children who had AD in the first years of life, 80% in Taiwanese children at the age of 6 years and lately 66.7% of Thai AD children at the age of 5 years.[13,14,16] In our study, 44% of AD patients had complete remission at the median age of 6.3 years. In early AD, 50% of AD patients had complete remission at the median age of 4.3 years. In Germany, 43.2% of early AD were in remission at the age of around 3 years.[12] The different age at remission can be due to the different definition of disease remission, genetic and environmental factors. The percentage of early AD in this study was 55.9%, which was less than previous reports in Thailand (64.6%).[16] Since early AD is one of the factors associated with remission, the lower number of early AD in our study could affect the lower remission rate. Moreover, house dust mite sensitization was found in 10.2% of AD by the study of Wananukul, *et al.* and 50% of persistent AD by the study of Guo, *et al.*[14,16] In our study, we found about 80% of AD with house dust must sensitization at school-age. The high rate of house dust mite sensitization at school-age might prolong the course of AD in our study. Quah, *et al.*, also reported that house dust mite sensitization (*Df*) was higher at 5 (44.3%) than at 2 years of age (16.2%). It also increased the risk of AR and asthma at the age of 5 years in patients with early onset eczema.[15]

Our study showed that patients with early AD had higher remission rate than later onset AD which was the same as the study by Guo and Wananukul, *et al.*[14,16] Illi, et al. showed that the severity of AD was a predictor of the natural course of disease. This concept was supported by the study of Wananukul *et al.*[12,16] However, our study did not show the effect of AD severity on remission rate, partly due to the small sample size. The other possibility is that we implemented intensive wet wrap as well as immunotherapy in moderate severity and could therefore induce remission in higher severity patients.[23,24]

Our study found that AR and asthma was diagnosed in 61.8% and 29.4% of the patients at the median age of 4.6 and 3.8 years, respectively. These numbers were higher than previous study in Thailand which revealed that the development of AR was 36% and asthma 9%, in AD children.[16] This could be due to the subjects in this study being recruited from an allergy clinic and respiratory symptoms being closely monitored in a longer follow-up period. The AR was found more in patients with later onset AD than in early onset, which was in concordance with the study by Wananukul, *et al.*[16] The risk of early asthma was early AD and history of food allergy. Early AD as a risk factor for wheezing in the first 3 years of life was supported by a German cohort.[12]

In conclusion, our study identified the natural history of AD, the risk factors associated with remission and progression to Atopic March. Almost half of AD children had complete remission at school age with a better prognosis in early AD. Two-thirds and one-third developed AR and asthma at preschool age, respectively. The most common aeroallergen sensitization was *Dp* and *Df*. Early AD and food allergy were predictors of early asthma.

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