ATOPIC DERMATITIS AT PEDIATRIC TERTIARY CARE CENTERS IN THAILAND: A MULTICENTER STUDY

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Abstract. Atopic dermatitis (AD) is the most common chronic inflammatory skin disease in children. The aim of this prospective study was to investigate the clinical characteristics and management of AD in patients aged ≤15 years who received care at the tertiary pediatric dermatology clinics in Thailand during January 2008 to March 2009. Of 560 included patients, the median age was 4.5 (range 0-15.2) years, and 298 (53.2%) were females. Age of onset was younger than two years in 410 (73.2%) patients. Concomitant asthma and allergic rhinitis (AR) were found in 59 (10.5%) and 206 (36.8%) of patients. Family history of AR was found in 276 (49.3%), AD in 175 (31.3%), and asthma in 134 (23.9%) patients. The common features were chronicity (97.6%), typical morphology with age-specific distribution (97.2%), pruritus (95.8%), xerosis (91.9%), and itch when sweating (78.8%). Using Rajka and Langeland severity grading, 30.9% of cases were mild, 51.8% were moderate, and 17.3% were severe. Factors significantly associated with severe AD were younger age at onset (p=0.03), history of cow's milk allergy (p=0.02), and food allergy (p=0.01). Exclusive breastfeeding for ≥6 months and early cow's milk exposure were not found to significantly correlate with disease severity or age of onset. Dry skin was the most common (79.8%) aggravating factor. Topical corticosteroids, calcineurin inhibitors, and antibiotics were prescribed in 90.0%, 12.9%, and 7.0% of patients, respectively. Early-onset AD should be closely monitored and aggressively controlled the aggravating factors.

Keywords: atopic dermatitis, children, Thailand

INTRODUCTION

Atopic dermatitis (AD) is the most common chronic pruritic inflammatory skin disease in children. The overall prevalence of AD was reported to be 15-30% (Bieber, 2010). The incidence of AD has increased in industrialized countries over the past several decades due to changes in lifestyle and the environment (Bieber, 2010). The clinical characteristics of AD vary according to genetic background, lifestyle, culture, and environment. The management of AD also varies from setting to setting according to differences in socioeconomic status, available therapies, and type of health care system (Rubel *et al*, 2013). Very few studies have been conducted in pediatric AD patients in Thailand.

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The aim of this study was to investigate the clinical characteristics and management of AD in patients aged 15 years or younger who received care at the tertiary pediatric dermatology clinics in Thailand. The findings from this study will help to guide the clinical management of pediatric AD patients in Thailand.

MATERIALS AND METHODS

This multicenter prospective study was conducted among 560 patients who received treatment for AD at 1 of 7 pediatric tertiary referral center in Thailand during January 2008 to March 2009. Patient data from 7 tertiary pediatric dermatology clinics were included in the analysis. Patients aged 15 years or younger who fulfilled Hanafin and Rajka criteria (Hanifin and Rajka, 1980) for diagnosis of AD were enrolled. Demographic data, history, symptoms, clinical signs, and management were recorded. Parents were queried regarding AD-related aggravating factors experienced by their children. Clinical severity of AD was evaluated using Rajka & Langeland severity grading (Rajka and Langeland, 1989). The institutional review board of each participating center approved the study protocol.

Data were analyzed using SPSS Statistics version 20 (IBM, Armonk, NY). Data were analyzed using descriptive statistics. Univariate analysis was performed using chi-square test. Multivariate analysis was performed using ordinal logistic regression to identify factors associated with disease severity. Data are presented as number and percentage, and odds ratio with 95% confidence interval. A p-value <0.05 was considered to be statistically significant.

RESULTS

A total of 560 AD patients were included. The median age of patients was 4.5 (range 0-15.2) years, and 298 (53.2%) were females. The median age of onset was 12 (range 0-156) months, and 410 (73.2%) patients had disease onset before 2 years of age. There were 173 (30.9%) patients classified as mild AD, 290 (51.8%) as moderate AD, and 97 (17.3%) as severe AD (Table 1).

The median duration of exclusive breastfeeding was 4 months (range 3 days-3 years), with 159 (28.4%) patients having been exclusively breastfed for at least 6 months. The median (range) age of AD onset was not different between patients who had exclusive breastfeeding for more than 6 months and those who had exclusive breastfeeding for less than 6 months [12.0 (0.0-120.0) *vs* 12.0 (0.0-125.0) months; p=0.49]. The median (range) age of AD onset was also not different between patients who had exposure to cow's milk before 6 months of age and those who were exposed to cow's milk after 6 months of age [12.0 (0.0-125.0) *vs* 9.0 (0.0-120.0) months; p=0.91]. Concomitant asthma and concomitant allergic rhinitis (AR) was found in 59 (10.5%) and 206 (36.8%) patients, respectively. Of these patients with concomitant allergic disease, 76.3% (45/59) of asthma patients and 64.6% (133/206) of AR patients were older than 5 years at the time of the study. The median onset age of asthma and AR was 24 months (range 0-120) and 24 months (range 0-156), respectively. The age at onset of AD was statistically younger than onset of asthma (p=0.03) and AR (p=0.01). Family history of atopic disease was found in 392 (70.0%) patients, as follows: 49.3% with AR, 31.3% with AD, and 23.9% with asthma. One hundred and forty-seven of 515 (28.5%) patients reported food intolerance. In those with food intolerance, 30.7% of them reported more than 1 food and 16.3% of them reported cow's milk allergy. The median (range) age of patients with food intolerance was not different from the median age of those without food intolerance [4.9 (0.2-15.2) *vs* 4.3 (0.0-15.2) months; p=0.07].

The most commonly clinical features were chronicity (97.6%), typical morphology with

Table 1
Demographic and clinical characteristics of pediatric patients.

Characteristics	Number (%)
Current age (years)	
0-1	136 (24.3)
>1-2	43 (7.7)
>2-5	122 (21.8)
>5-15	259 (46.2)
Concomitant allergic diseases	
Allergic rhinitis and/or asthma	225 (40.2)
Allergic rhinitis	206 (36.8)
Asthma	59 (10.5)
Family history of allergic diseases	
Any allergic diseases	392 (70.0)
Allergic rhinitis	276 (49.3)
Atopic dermatitis	175 (31.3)
Asthma	134 (23.9)
Feeding history	
Exclusive breastfeeding <6 months	239 (42.7)
Exclusive breastfeeding ≥6 months	159 (28.4)
Cow's milk exposure since birth	150 (26.8)
Rajka & Langeland's severity score[a]	
Mild (3-4)	173 (30.9)
Moderate (4.5-7.5)	290 (51.8)
Severe (8-9)	97 (17.3)

[a] Rajka & Langeland's severity score was based on clinical signs and symptoms (Rajka and Langeland, 1989).

age-specific distribution (97.2%), pruritus (95.8%), xerosis (91.9%), and itch when sweating (78.8%). The features according to Hanifin and Rajka criteria are shown in Table 2. Dry skin was the most commonly reported aggravating factor (79.8%). Regarding the season when patients reported being most affected by AD, 50.4% reported summer and 40.0% reported winter (Table 3). The 59 (10.5%) patients who reported that emotions had the effect of aggravating AD were younger than the patients who did not [median (range) age 2.8 (0.3-15.2) *vs* 4.8 (0.0-15.2) months; p=0.02].

Two hundred and seventy-seven of 560 (49.5%) patients reported having been treated at a tertiary care clinic of a governmental hospital within the last 5 years, and 322 (57.5%) patients had a history of having been treated at more than one center. Patients with more severe disease sought care at alternative hospitals more often than those with less severe disease (p=0.01) due to treatment dissatisfaction.

Table 2
History and physical findings of all cases according to Hanifin and Rajka criteria.

Features	Number positive/Total (%)
Major features	
Chronic or chronically-relapsing dermatitis	540/553 (97.6)
Typical morphology and age-specific pattern	520/535 (97.2)
Pruritus	526/549 (95.8)
Personal or family history of atopy	391/536 (72.9)
Minor features	
Xerosis	499/543 (91.9)
Itch when sweating	427/542 (78.8)
Early age of onset	410/560 (73.2)
Elevated serum IgE	67/129 (51.9)
Orbital darkening	257/522 (49.2)
Pityriasis alba	205/525 (39.0)
Course influenced by environmental/emotional factors	193/520 (37.1)
Immediate (type I) skin test reactivity	41/120 (34.2)
Food intolerance	147/515 (28.5)
Anterior neck folds	141/519 (27.2)
Perifollicular accentuation	141/519 (27.2)
Ichthyosis	141/522 (27.0)
Dennie-Morgan infraorbital fold	138/521 (26.5)
Facial pallor/facial erythema	130/517 (25.1)
Tendency toward cutaneous infections	116/516 (22.5)
Intolerance to wool and lipid solvents	111/498 (22.3)
Tendency toward non-specific hand or foot dermatitis	102/519 (19.7)
Cheilitis	101/526 (19.2)
Recurrent conjunctivitis	87/531 (16.4)
White dermographism/delayed blanch	40/456 (8.8)
Nipple eczema	16/523 (3.1)
Anterior subcapsular cataracts	8/358 (2.2)
Keratoconus	0/352 (0.0)

The primary care physicians for these patients were dermatologists in 31.8%, pediatricians in 31.5%, pediatric dermatologists in 18.0%, general practitioners in 13.8%, and other types of physicians in 4.9% of cases. Topical medications used since AD onset to the time of the study included: topical corticosteroids (TCS) in 504 (90.0%) patients; calcineurin inhibitors

Table 3
Aggravating factors of atopic dermatitis (*N*=560).

Factors	Number positive (%)
Dry skin	447 (79.8)
Seasonal change	427 (76.3)
Summer season	282 (50.4)
Winter season	224 (40.0)
Rainy season	27 (4.8)
Dust	205 (36.6)
Foods[a]	176 (31.4)
Furry pets	69 (12.3)
Emotional change	59 (10.5)
Furry toys	51 (9.1)
Cigarette smoke	24 (4.3)
Skin infection	5 (0.9)

[a] Foods: egg yolk, egg white, soy bean, seafood, peanut, etc.

(TCI) in 72 (12.9%) patients; and, antibiotics in 39 (7.0%) patients. There were 4 (0.7%) patients who received systemic corticosteroids and 1 (0.2%) patient that received phototherapy. Antihistamines were prescribed in 504 (90%) patients, and 54.8% of them were sedating antihistamines. Of the 473 patients with data available about skin care advice and counseling, 88 (18.6%) of families stated that they did not receive instruction about skin care.

On univariate analysis, factors associated with disease severity were early onset of AD (p=0.03), positive history of cow's milk allergy (p=0.02), and food allergy (p=0.01). No significant association was found between disease severity and duration of exclusive breastfeeding for at least 6 months (p=0.06), cow's milk exposure before 6 months of age (p=0.17), or having concomitant AR and/or asthma (p=0.32). On multivariate analysis, history of food allergy was the only independent factor significantly associated with disease severity (p=0.01) (Table 4).

DISCUSSION

This study set forth to investigate the clinical characteristics and management of AD in children who received dermatologic care at tertiary care centers in Thailand. More than two-thirds of the AD patients evaluated in this study had moderate to severe disease. Most patients had onset of AD before the age of two, and this factor was found to be significantly associated with disease severity. Concomitant atopic disease was found in almost half of patients with later onset. Family history of atopic diseases was found in up to 70% of patients. TCS was the most commonly used topical medication, with TCI being used infrequently. No protective association was observed between exclusive breastfeeding and onset or severity of AD.

Consistent with the findings of our study, onset of AD was reported to start usually in infancy or early childhood (Bieber, 2010; Baron *et al*, 2012; Eichenfield *et al*, 2014b; Thomsen, 2014; Pyun, 2015). Our findings also confirmed previous studies that reported no evidence of a protective effect of exclusive breastfeeding against the development of childhood AD (Eichenfield *et al*, 2014b; Sidbury *et al*, 2014; Thomsen, 2014; Madhok *et al*, 2015; Oszukowska *et al*, 2015). Neither early cow's milk exposure nor duration of breastfeeding was found to affect the onset of AD. Previous studies reported that disease severity was not altered or affected by breastfeeding for at least 6 months or by early exposure to cow's milk (Sidbury *et al*, 2014; di Mauro *et al*, 2016). Even though prolonged breastfeeding may not delay AD onset or decreased disease severity, exclusive breastfeeding for at least 4 to 6 months of life is still recommended for its nutritional and immunological benefits (Eichenfield *et al*, 2014b; Oszukowska *et al*, 2015).

Similar to many studies, concomitant personal and/or familial history of atopic diseases was found frequently in this study. The onset

Table 4
Factors associated with atopic dermatitis severity.

Factors	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Early onset of atopic dermatitis	0.99 (0.99-1.00)	0.03	0.99 (0.99-1.00)	0.08
Concomitant allergic disease (asthma and/or allergic rhinitis)	1.18 (0.85-1.62)	0.32		
History of food allergy	2.00 (1.40-2.86)	0.01	2.07 (1.42-3.03)	0.01
History of cow's milk allergy	1.10 (1.01-1.18)	0.02	1.08 (0.99-1.18)	0.08
Exclusive breastfeeding more than 6 months	0.69 (0.47-1.02)	0.06		
Cow's milk exposure before 6 months of age	0.78 (0.55-1.11)	0.17		

of other atopic diseases was found to occur later than the onset of AD (Ring *et al*, 2012; Eichenfield *et al*, 2014b). In this study, about one-third of parents reported food allergy in their AD-affected child, and this was found to be a common parental concern (Sidbury *et al*, 2014). Food allergy could aggravate AD lesions in a small percentage of infants and young children (Boyce *et al*, 2010). From our data, serum specific IgE was found in half of all patients. This finding indicates allergen sensitization and this data should be interpreted using clinical correlations (Boyce *et al*, 2010; Greenhawt, 2010; Suh, 2010). Food allergy evaluation should be considered in children younger than 5 years who have persistent or severe AD – particularly in those with immediate cutaneous reaction after ingestion of a specific food (Boyce *et al*, 2010).

Given the absence of pathognomonic signs or specific diagnostic laboratory markers, the diagnosis of AD is based mainly on clinical features. The diagnosis of AD requires the exclusion of other skin conditions that share similar signs and symptoms. Several sets of diagnostic criteria with various sensitivities and specificities have been developed to diagnose AD (Hanifin and Rajka, 1980; Williams *et al*, 1994; Wisuthsarewong and Viravan, 2004; Ring *et al*, 2012; Wollenberg *et al*, 2016). Many characteristics of AD from Hanifin and Rajka criteria, including pruritus, typical age-specific pattern, chronicity, and xerosis, were commonly found in Thai children (Wisuthsarewong and Viravan, 2004). Some minor criteria, such as pityriasis alba, allergic shiner, orbital darkening, anterior neck folds, and nonspecific hand or foot dermatitis, have been noted to be nonspecific (Hanifin and Rajka, 1980; Wisuthsarewong and Viravan, 2004). In this study, the incidence of keratoconus and cataract was rare. These two conditions were mostly found in chronic severe cases.

Many factors that could aggravate AD lesions were identified in this report. Consistent with our findings, cigarette smoke and skin infection were not found to be common aggravating factors among AD patients in Thailand (Wisuthsarewong and Viravan, 2004). Skin infection, most notably from *Staphylococcus aureus*, was an important aggravating factor, but it often went unrecognized by parents.

The mainstay of treatment for AD is good skin care to restore the impaired skin barrier, control inflammation, and reduce pruritus (Ring *et al*, 2012; Eichenfield *et al*, 2014a). When deciding

on a treatment for AD, patient age, compliance, economic background, and quality of life must be taken into consideration. Regular application of moisturizer to prevent dry skin, the most frequent aggravating factor, should be emphasized (Rubel *et al*, 2013; Sidbury *et al*, 2014). The high cost of moisturizer with anti-inflammatory effect may restrict or prohibit their use. Most physicians still use TCS as the first-line therapy. To minimize potential side effects, the lowest potency of TCS that can control symptoms should be used. Intermittent use of low- to moderate-potency TCS was generally well-tolerated, but close monitoring for side effects was recommended (Lyons *et al*, 2015; Saeki *et al*, 2016). TCI may be useful in patients requiring long-term treatment on sensitive areas, such as the face and skin folds, which are areas where prolonged use of TCS would not be appropriate (Rubel *et al*, 2013; Eichenfield *et al*, 2014a; Saeki *et al*, 2016; Wollenberg *et al*, 2016). Immunosuppressive drugs, including cyclosporine, mycophenolate mofetil, methotrexate, and azathioprine, demonstrated efficacy in recalcitrant cases; however, these drugs were rarely used in this study.

Previous studies reported that approximately 60% to 70% of childhood-onset AD spontaneously resolved before adolescence (Thomsen, 2014; Pyun, 2015). Effective parental education about AD will improve treatment compliance, disease severity, and patient quality of life (Bieber, 2010; Rubel *et al*, 2013; Sidbury *et al*, 2014; Wollenberg *et al*, 2016). However, about one-fifth of parents in this study reported that they did not receive instruction about AD, and treatment. It is important for physicians to spend sufficient time to explain the nature of AD, its potential aggravating factors, and treatment protocols that must be carefully followed to control the disease.

The findings of our study should be interpreted with awareness, given that they may not be generalizable to all settings in Thailand. However, this study was conducted in patients that attended the tertiary referral centers from more than one region of Thailand. As such, included cases were often advanced and recalcitrant. Given the size of our sample and the range of severity, we are sufficiently confident that these results are representative of AD across Thailand. The findings from this study will help to guide the clinical management of pediatric AD in Thailand.

In conclusion, most children with severe AD had early age of onset. Appropriate skin care, effective control of inflammation, and measures to prevent important aggravating factors are recommended.

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CONFLICTS OF INTEREST

The authors hereby declare no conflicts of interest regarding any aspect of this study.

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