

Seasonal variation and monthly patterns of skin symptoms in Korean children with atopic eczema/dermatitis syndrome

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ABSTRACT

Background: There have been controversies about the seasonality in aggravation of atopic eczema/dermatitis syndrome (AEDS) symptoms, although understanding the seasonal patterns of AEDS symptoms is an important step in preventing exacerbation through proactive management.

Objective: The aim of this study was to evaluate whether there are seasonal variations or monthly patterns of symptoms in children with AEDS.

Methods: A total of 590 children with AEDS (median age, 21 months) were enrolled and were followed up for at least 1 year between August 2012 and March 2015. Daily symptom scores that described the extent of itching, sleep disturbance, erythema, dryness, oozing, and edema were recorded on a scale of 0 to 4. The baseline score for each patient was defined as the 20th percentile of each individual's total score. The symptom score difference of each patient was expressed relative to the baseline level. The seasonal or monthly variation in symptom score differences was analyzed through generalized estimating equation analysis.

Results: Based on the AEDS symptom records from 87,879 person-days, the mean symptom score difference from baseline in patients with AEDS increased significantly in spring, autumn, and winter relative to the reference season (summer): by 0.62 (95% confidence interval [CI], 0.44–0.81) in spring, by 0.45 (95% CI, 0.24–0.67) in winter, and by 0.18 (95% CI, 0.02–0.36) in autumn. The mean symptom score difference from baseline increased significantly in January, February, March, April, May, June, October, November, and December relative to the reference month of August.

Conclusion: Skin symptoms in children with AEDS were worse in spring, winter, and autumn than in summer. In terms of monthly patterns, the skin symptoms were the worst in April.

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Atopic eczema/dermatitis syndrome (AEDS) is a chronically relapsing skin disease characterized by pruritus and sleep disturbance. The chronic and frequent relapses affect the quality of life of both patients and their parents.^{1–4} AEDS represents an aggregation of several subtypes of diseases, with certain clinical and biologic characteristics, such as allergic AEDS and nonallergic AEDS.⁵ Although patients with allergic AEDS have elevated specific immunoglobulin E (IgE) antibodies against food or inhalant allergens, nonallergic AEDS do not have atopic features.^{6–8} IgE responses are not necessary for the development of

AEDS but may be associated with disease flares.⁶ The T lymphocyte system, specific interleukins pathway, and gene polymorphism also play a crucial role on the diverse clinical features of AEDS.^{9,10}

The reasons for AEDS symptom aggravation are variable and complex. There have been controversies about the seasonality in aggravation of AEDS symptoms. An observational study demonstrated that AEDS flares were correlated with damp and hot weather.¹¹ In a cohort study, AEDS was classified into summer and winter types, depending on whether patients exhibited severe skin symptoms during summer and winter.¹² However, those studies had limitations in representing seasonality related to their small sample sizes and short observation periods. There has not yet been a panel study in which individual patients were followed up in every season through daily evaluation of skin symptoms.

The Republic of Korea is located in the middle latitudes of the northern hemisphere, on the east coast of the Eurasian continent, adjacent to the western Pacific.¹³ It displays complex climate characteristics, with both continental and oceanic features, as well as four distinct seasons.¹³ The hottest month is August,

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Table 1 Characteristics of the study subjects
(N = 590)

Variables	
Boys, no. (%)	362 (61.4)
Age, mean $\pm$ SD, mo	40.1 $\pm$ 44.4
BMI, mean $\pm$ SD, kg/m ²	17.0 $\pm$ 2.2
Age at AEDS occurrence, mean $\pm$ SD, mo	13.1 $\pm$ 21.7
SCORAD at initial visit, mean $\pm$ SD	17.1 $\pm$ 12.6
Sensitization to allergens, no. (%) (n = 571)	405 (70.9)
Food (n = 548)	310 (56.6)
Inhalant (n = 233)	147 (63.1)
Residential area, no. (%)	
Seoul and metropolitan area	538 (91.2)
The other areas	52 (8.8)

SD = Standard deviation; BMI = body mass index; AEDS = atopic eczema/dermatitis syndrome; SCORAD = scoring atopic dermatitis.

whereas January is the coldest month.^{13,14} The humidity is the highest in July, which reaches 80–90% nationwide, whereas the lowest humidity levels are 30–50%, in the period from January to April.^{13,14} Understanding the seasonal patterns of AEDS symptoms is an important step in preventing exacerbation through proactive management. Therefore, we performed this panel study by using a daily symptom diary to evaluate whether seasonal variation and monthly patterns in skin symptoms occurred in children with AEDS.

METHODS

Study Population and Study Design

We enrolled 590 patients, ages $\leq$ 17 years, who had AEDS and who were followed up for at least 1 year between August 2012 and March 2015 (Table 1). AEDS was diagnosed based on Hanifin and Rajka criteria, and the severity was evaluated by using the Scoring Atopic Dermatitis.^{15,16} All the patients were instructed to bathe once daily in warm water for $\sim$ 10 minutes and to apply moisturizers frequently during the study period. We offered 1% hydrocortisone or prednisolone valeroacetate for patients who required topical corticosteroids (TCS) as a rescue medicine and asked the patients to cover a body area equivalent to two hands by using one fingertip unit of TCS. Systemic corticosteroids, immunosuppressants, and phototherapy were not allowed during the study period.

The parents were instructed to keep a symptom diary that described the extent of itching, sleep disturbance, erythema, dryness, oozing, and edema on

a scale of 0 (mild) to 4 (severe). TCS usage was also recorded when it was used as rescue medicine. The baseline score of each patient was defined as the 20th percentile of the individual's total AEDS symptom score. The symptom score difference of each patient was expressed relative to the baseline level to reflect the change in skin symptoms. If the symptom score was less than or equal to the baseline score, then the score difference was expressed as zero. The mean symptom score difference from baseline was calculated by determining the daily change in symptom score from baseline for each subject and then calculating the mean for all of the subjects during the season or month in question. Data on daily outdoor temperature, relative humidity, and precipitation were obtained from the Korean Meteorological Administration (Table 2).¹⁴ This study was approved by the institutional review board at Samsung Medical Center, Seoul, Korea.

Laboratory Tests

Blood samples were collected at the initial visit. The serum specific IgE antibodies to *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, egg white, cow's milk, wheat, soy, and peanut were measured with the ImmunoCAP system (Thermo Fisher Scientific Inc., Waltham, MA), and concentrations of $\geq$ 0.35 kU/L were used to determine whether the patient was sensitized. The skin-prick test (SPT) was performed by using a standard method.¹⁷ Commercial extracts (all from Allergopharma, Reinbek, Germany) of the following common allergens were used: House-dust mites (*D. pteronyssinus* and *D. farinae*), molds (*Alternaria*, *Aspergillus*, *Cladosporium*, and *Penicillium*), pollen (timothy, Bermuda, meadow grass, alder, birch, elder, oak, Japanese cedar, ragweed, mugwort, short ragweed, Japanese hops, pine, and fat hen), animal dander (dog and cat), and cockroach. Histamine and isotonic saline solution were used as positive and negative controls, respectively. A positive SPT result was defined as a mean wheal diameter of $\geq$ 3 mm. Of 571 patients who received blood tests or SPTs, 405 patients (70.9%) were sensitized to at least one of the food or inhalant allergens (Table 1).

Statistical Analysis

Data were analyzed with SAS version 9.1 software (SAS Institute, Cary, NC) and were presented as the mean $\pm$ standard deviation. A generalized estimating equation (GEE) analysis model was used to assess the association between each season or month and the AEDS symptoms. Data for the first 3 months were excluded from analysis because they may not have reflected the patterns of seasonality during the initial period of proper treatment. Seasons were defined according to the meteo-

Table 2 Nationwide monthly levels of outdoor daily temperature, humidity, and precipitation during the study period

Month	Outdoor Temperature, °C			Outdoor Humidity, %			Precipitation, mm		
	Mean	Minimum	Maximum	Mean	Minimum	Maximum	Mean	Minimum	Maximum
1	−0.1	−9.3	6.5	62.1	36.6	90.7	2.7	0	45.1
2	1.8	−7.9	9.1	61.2	36.9	90.7	4.4	0	146.0
3	7.0	−1.6	15.3	57.9	34.9	85.0	7.3	0	145.1
4	11.7	5.0	16.9	60.0	43.8	87.3	8.0	0	180.4
5	17.9	11.3	23.9	63.5	46.6	91.1	11.6	0	183.5
6	21.9	18.8	24.7	75.3	62.1	91.8	7.4	0	191.0
7	25.4	21.2	27.6	79.9	61.8	90.2	13.2	0	225.0
8	25.6	20.9	29.5	80.0	67.8	93.3	19.7	0	308.9
9	20.6	15.9	24.1	77.2	61.7	92.9	15.1	0	253.0
10	14.9	8.3	22.4	71.0	52.3	92.2	11.2	0	151.5
11	7.6	−1.3	15.1	66.6	47.5	91.3	5.2	0	81.5
12	0	−7.5	5.9	64.1	45.6	88.1	3.1	0	106.0

rologic definition of winter as December-February, spring as March-May, summer as June-August, and autumn as September-November.

GEE models were constructed to explore the influence of season and month on symptom score differences after adjustment for age, sex, and body mass index (BMI). We also analyzed the seasonal pattern of the frequency of TCS application by using GEE models after adjusting for age, sex, and BMI. In addition, we performed subgroup analysis based on the age group (0–2, 3–5, and ≥ 6 years old). We also analyzed whether there was a difference in the seasonal or monthly patterns of skin symptoms between patients with allergic AEDS and patients with nonallergic AEDS. Because the use of separate univariate tests leads to an inflated type 1 error, the Bonferroni correction was applied to subgroup analysis. A p value <0.05 was considered significant.

RESULTS

Of the symptom records for 87,879 person-days, 18,176 were taken in spring, 20,898 in summer, 23,976 in autumn, and 24,829 in winter. Symptom diaries were filled out on an average of 212.9 ± 164.0 days. When summer was used as the reference season, the mean symptom score difference from baseline increased significantly in spring, autumn, and winter in the unadjusted GEE models: By 0.62 (95% confidence interval [CI], 0.44–0.80) in spring, by 0.46 (95% CI, 0.24–0.68) in winter, and by 0.19 (95% CI, 0.02–0.36) in autumn. After adjusting for age, sex, and BMI, the mean symptom score difference from baseline in the GEE models also increased in spring, autumn, and winter relative to summer: By 0.62 (95% CI, 0.44–0.81) in spring, by 0.45 (95% CI, 0.24–0.67) in winter, and by 0.18 (95% CI, 0.02–0.36) in autumn (Fig. 1).

The monthly pattern was analyzed with August as the reference month. The mean symptom score difference increased significantly in January, February, March, April, May, June, October, November, and December relative to August in the adjusted GEE models: By 0.55 (95% CI, 0.28–0.81) in January, by 0.58 (95% CI, 0.3–0.85) in February, by 0.76 (95% CI, 0.51–1.01) in March, by 0.77 (95% CI, 0.50–1.05) in April, by 0.64 (95% CI, 0.40–0.88) in May, by 0.30 (95% CI, 0.08–0.52) in June, by 0.04 (95% CI, −0.10 to 0.19) in July, by 0.16 (95% CI, 0–0.32) in September, by 0.32 (95% CI, 0.08–0.55) in October, by 0.40 (95% CI, 0.15–0.65) in November, and by 0.56 (95% CI, 0.31–0.81) in December (Fig. 2).

When analyzing TCS usage from the symptom diaries, we found that 43.7% of the patients used TCS in spring, 37.0% in summer, 38.1% in autumn, and 37.6% in winter. When the frequency of TCS usage was analyzed in different seasons in the GEE models, it was apparent that patients applied TCS more frequently in spring than in summer, autumn, and winter. When spring was used as the reference season, the odds ratios for summer, autumn and winter were 0.76 (95% CI, 0.65–0.88), 0.79 (95% CI, 0.67–0.94), and 0.78 (95% CI, 0.68–0.89), respectively.

Subgroup analysis was performed after the subjects were divided into three age groups (0–2, 3–5, and ≥ 6 years old) and children ages 0–2 years showed significant seasonal variation in symptom scores (Fig. 3). In children ages ≤ 2 years, the mean symptom score difference from baseline in the GEE models after adjustment for sex and BMI increased in spring, winter, and autumn relative to summer: By 0.70 (95% CI, 0.45–0.96) in spring, by 0.61 (95% CI, 0.32–0.91) in winter, and by 0.30 (95% CI, 0.08–0.53) in autumn. However, no statistical significance

Figure 1. Seasonal patterns of skin symptoms in patients with atopic eczema/dermatitis syndrome; data are presented as mean symptom score differences from baseline with 95% confidence intervals; the baseline symptom score was defined as the 20th percentile of the individual symptom score; seasonal variation was analyzed by using generalized estimating equation analysis, and summer was used as the reference season. * $p < 0.05$.

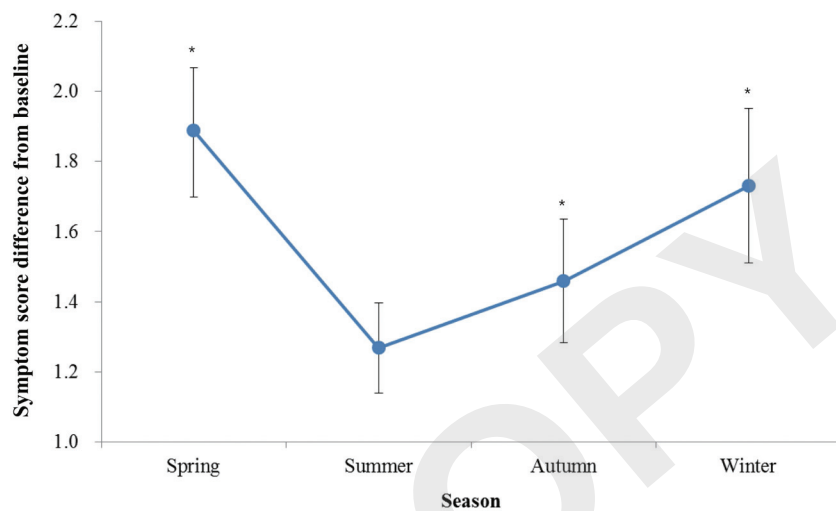
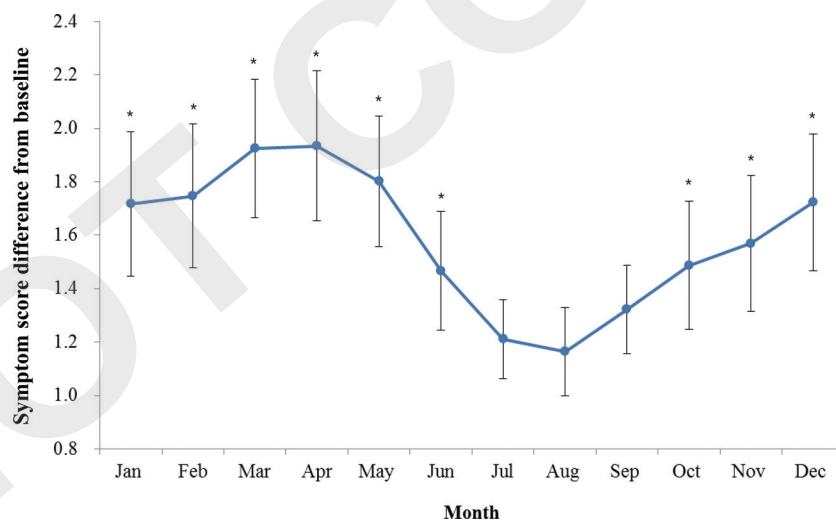


Figure 2. The monthly pattern of skin symptoms in patients with atopic eczema/dermatitis syndrome; data are presented as mean symptom score differences from baseline, with 95% confidence intervals; the baseline symptom score was defined as the 20th percentile of the individual symptom score; monthly variation was analyzed by using generalized estimating equation analysis, and August was used as the reference month. * $p < 0.05$.



was found in seasonal variation of AEDS symptoms in children ages ≥ 3 years. The mean symptom score difference from baseline in the adjusted GEE models in children ages 3–5 years increased in autumn, spring, and winter relative to summer: By 0.38 (95% CI, -0.04 to 0.79) in autumn, by 0.36 (95% CI, -0.01 to 0.72) in spring, and by 0.18 (95% CI, -0.17 to 0.88) in winter. The mean symptom score difference from baseline in the adjusted GEE models in children ages ≥ 6 years increased in spring but decreased in autumn and winter relative to summer, with mean differences of 0.35 (95% CI, -0.31 to 1.00) in spring, -0.12 (95% CI, -1.00 to 0.76) in autumn, and -0.21 (95% CI, -0.90 to 0.49) in winter. Except for 19 patients who refused or who had a failed test result, 571 patients were examined for allergen sensitization (Table 1). There was no significant difference in the seasonal or monthly patterns of skin symptoms between patients with allergic and those with nonallergic AEDS.

DISCUSSION

To the best of our knowledge, this is the largest panel study of seasonal and monthly patterns of skin symptoms in children with AEDS. This study was designed to continuously record eczema symptoms in patients with AEDS over the course of a year by using a symptom scoring system for statistical analysis. We investigated the relationship between symptoms and seasons after excluding the first 3 months of symptom data, during which appropriate treatment had not yet been administered. In addition, we analyzed symptom score differences from the baseline level to monitor the change in symptoms. Because AEDS is a chronic inflammatory disease, skin symptoms wax and wane from an individual's baseline symptomatic state rather than worsen from an asymptomatic state. Therefore, we analyzed variations in symptom scores based on each individual's 20th percentile symptom score. Our study revealed that skin symptoms in children with AEDS were worse in spring, winter, and autumn than

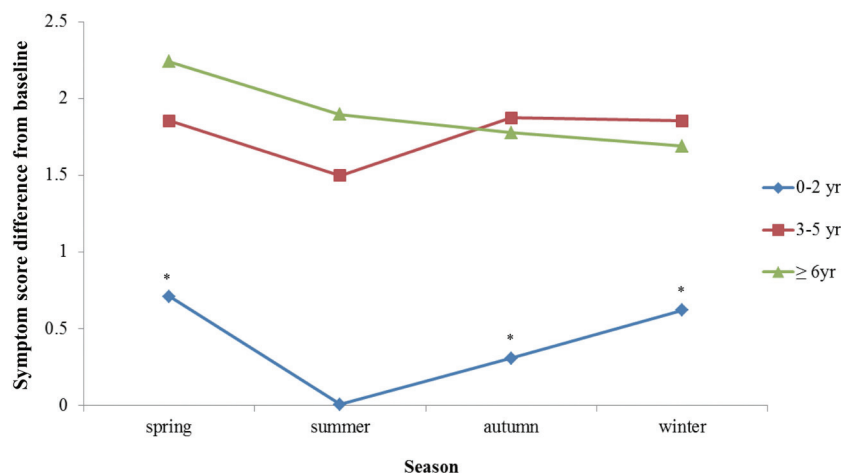


Figure 3. Seasonal pattern of mean symptom score differences from baseline in different age groups: 0–2, 3–5, and ≥ 6 years old; seasonal variation was analyzed by using generalized estimating equation analysis, and summer was used as the reference season for each age group. * $p < 0.05$.

in summer. Skin symptom scores were higher in January, February, March, April, May, June, October, November, and December than in August. We also found that the patients applied TCS as rescue medicine more frequently in spring than any other season, which indicated that symptoms were worse during spring.

Several conflicting reports have been published regarding seasonal variation in AEDS symptoms.^{11,12,18–21} A previous U.S. study indicated that patients with AEDS were more likely to have higher Investigator Static Global Assessment scores in winter than in spring.²² Moreover, the patients with AEDS had a poorer response to TCS treatment in winter than in spring.²² Another study, of 682 Japanese patients with AEDS, demonstrated that 66% (452/682) experienced seasonal deterioration of skin lesions, and the overall incidence of deterioration in spring, summer, autumn, and winter was 25, 19, 11, and 36%, respectively.²¹ However, there were no objective measures of symptom aggravation in that study because the data were drawn from individual self-reported questionnaires. Indeed, most studies used questionnaires, and, thus, the degree of seasonal deterioration was difficult to quantify objectively.^{19,21,23,24}

The worsening of AEDS symptoms in spring, winter, and autumn relative to summer could be attributed to several environmental factors, including air pollution, pollen, and meteorologic factors.^{25–29} The mean seasonal levels of particulate matter (PM) with a diameter of $<2.5 \mu\text{m}$ and PM with a diameter of $<10 \mu\text{m}$ are much higher in spring and winter than in summer and fall.²⁶ In particular, Korea is subject to heavy dust storms from March to May because the springtime peak in PM coincides with Asian dust from Chinese and Mongolian deserts.²⁶ Air pollutants such as PM, formaldehyde, and volatile organic compounds impair the function of the epidermal barrier, which thus exacerbates AEDS symptoms.^{27,30}

Flare-ups of eczema might also occur after exposure to pollen. Grass pollen exposure by using an

environmental challenge chamber induced a significant exacerbation of skin lesions, with an increase of CCL17, CCL22, and IL-4 levels in patients with AEDS sensitized to pollen.²⁸ Unfortunately, we could not evaluate pollen sensitization in all of the patients. In addition, the low humidity levels and temperatures of spring and winter could cause skin barrier dysfunction and increase the incidence of flare ups in patients with AEDS.^{29,31,32} Healthy adults who were exposed to low humidity levels or low temperatures for several hours displayed reduced skin hydration, additional itchy-skin symptoms and dermatitis-like skin lesions, and greater susceptibility to mechanical stress.^{29,31–33}

Subgroup analysis in the present study revealed that infants ages 0–2 years showed seasonal variability in AEDS symptoms but children > 2 years did not. This might be explained by the progressive maturation of skin barrier function with age. Transepidermal water loss decreases and stratum corneum thickness increases from birth until 4 years of age.³³ Mature barrier function could protect the skin from aggravating factors, including cold and dry weather. Different time activity patterns might also influence exposure to various seasonal effects on AEDS symptoms.³⁴

One limitation of this study was that we did not collect objective data regarding skin hydration or skin barrier function on a daily basis because not all of the participants could handle medical instruments at home. In addition, the exact causes of seasonal variation were not identified, although various factors might worsen skin symptoms in patients with AEDS. Nevertheless, our results provided useful information on the seasonal and monthly patterns of AEDS symptoms that can be used in the creation of individualized management plans, depending on the season or month. Future studies will be needed to identify aggravating and mitigating factors that are particularly relevant to skin symptoms in each season.

CONCLUSION

We found that skin symptoms in children with AEDS were worse in spring, winter, and autumn than in summer. Symptoms were particularly exacerbated from March to May. Understanding seasonal patterns in symptom severity will help patients with AEDS to prevent deterioration through careful management before flare-ups.

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