Research Article

Relationship Between the Presence of Eczema Herpeticum and the Significance of Clinical and Laboratory Tests in Korean Children With Atopic Dermatitis

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Abstract

Background: Eczema herpeticum (EH) is a herpes simplex virus (HSV) infection superimposed on atopic dermatitis (AD).
Objectives: The aim of this study was to evaluate the relationship between clinical features and laboratory tests, including skin cultures, total IgE, eosinophil count, eosinophil cationic protein, and 25-hydroxyvitamin D_3 (25-(OH)D3), in Korean children with AD according to the presence of EH.
Patients and Methods: We enrolled 380 patients aged 6 months to 18 years who were admitted to Busan St. Mary's hospital from January 2012 to December 2014. All 380 subjects were divided into two groups: the control and the AD group. The AD group was further divided into two subgroups: EH^+ and EH^-.
Results: The male gender was related to the presence of EH (odds ratio of 2.56; 95% confidence interval, 1.19 - 5.53, P = 0.01), but age and 25-(OH)D_3 levels were not. After adjusting for age, gender, and 25-(OH)D_3, no significant relationship was found between total IgE, eosinophil cationic protein or eosinophil count levels and the presence of EH. The relationship between positive skin cultures and the presence of EH was significant (P < 0.001) and the presence of methicillin-resistant *Staphylococcus aureus* (MRSA) was also related to the development of EH (OR, 0.19; 95% CI, 0.04 - 0.92, P = 0.03).
Conclusions: We conclude that while male gender, positive skin culture results, and the presence of MRSA are factors influencing EH, serum 25-(OH)D_3 levels are not associated with EH in Korean AD children.

Keywords: Atopic Dermatitis, Eczema Herpeticum, Serum 25-(OH)D_3

1. Background

Atopic dermatitis (AD) is a most common chronic inflammatory skin disease causing intense irritation and pruritus in children (1, 2). The number of AD patients seems to be on the rise in many developing countries, affecting over 10% of the population, while approximately 20% of people in developed countries are affected with AD (3-5).

Many complications from recurrent bacterial and viral skin infections accompany AD (6), including eczema herpeticum (EH) which is a herpes simplex virus (HSV) infection superimposed on AD. The incidence of EH is as low as between 3% and 6% in patients with AD (7, 8). EH usually presents as a disseminated eruption of dome-shaped monomorphic vesicles that contain multinucleated giant cells infected with HSV. It can be associated with significant systemic complications, such as keratoconjunctivitis, as well as multi-organ involvement like meningitis and encephalitis (9). The risk of advancing EH is known to be highest in children younger than 3 years of age, with an even male-to-female ratio. According to the data, this seemingly rare disease has recently increased in the population (10). EH is a potentially fatal condition, so patients with EH require immediate and effective antiviral therapy (11). However, even though it is a serious and increasingly prevalent disease, only a few studies have investigated a large number of patients with EH. Research on the relationship between clinical features and laboratory tests including 25-hydroxyvitamin D3 (25-(OH)D_3) levels in AD children with and without EH are rare (12, 13).

2. Objectives

The aim of this study was to evaluate the relationship between clinical features and laboratory tests, including skin cultures, total IgE, eosinophil count, eosinophil cationic protein, and 25-(OH)D_3 in Korean children with AD according to the presence of EH.

3. Patients and Methods

3.1. Participants

This study was carried out on 380 patients aged 6 months to 18 years who were admitted to the pediatric department of Busan St. Mary hospital, Busan, Korea, between January 2012 and December 2014. The retrospective data collected from their individual medical records included demographic characteristics, historical features, and clinical features (fever, systemic symptoms, eye involvement, and type of eruption). In this study, fever was

defined as a temperature $\geq 38°C$ and systemic symptoms included headache, anorexia, or lethargy. Eye involvement was defined as keratoconjunctivitis diagnosed by an ophthalmologist. All participants with a history of taking any vitamin D or calcium supplements or drugs that could influence the serum 25-(OH)D_3 level, such as glucocorticoids and anti-epileptic drugs, and those who had chronic diseases or received phototherapy within the past 6 months were excluded.

The control group was composed of 130 patients with no history of allergic diseases such as allergic rhinitis, bronchial asthma, and urticaria. The AD group included 250 children who were diagnosed with AD by an allergy specialist at Busan St. Mary hospital according to the diagnostic criteria proposed by Hanifin and Rajka (14). Using the scoring atopic dermatitis (SCORAD) index, AD subject was classified as mild (< 15), moderate (15 - 9.9), or severe (≥ 40) (15).

The diagnosis of EH was made clinically by the same allergy specialist or dermatologist at the clinic. EH was also diagnosed by polymerase chain reaction for viral DNA obtained from blister fluid. Additionally, electron microscopy and immunofluorescence testing were used to identify HSV-infected cells. Depending on the presence of EH and including the patient's history, the AD group was divided into two subgroups: EH$^+$ and EH$^-$.

3.2. Laboratory Tests

During the examination, blood samples were collected and centrifuged at admission. Serum 25-(OH)D_3 level was assayed using an enzyme immunoassay kit (immunodiagnostic systems, COBAS 6000 Roche, Mannheim, Germany). For a descriptive analysis, we categorized the serum 25-(OH)D_3 levels into three classes: deficient (< 20 ng/mL), insufficient (20 - 29.9 ng/mL), or sufficient (≥ 30 ng/mL) (16).

Levels of eosinophil cationic protein (ECP), total IgE, and specific IgE (sIgE) for allergens were measured using Immuno CAP 250 (Thermo Fisher Scientific, Uppsala, Sweden). A total eosinophil count was measured with an automated hematology analyzer (coulter counter STKS; Beckman Coulter, Fullerton, CA, USA) using blood samples collected in EDTA tubes.

Before treatment, a skin swab test was performed on inflamed, pus-filled, or oozing areas. One swab was collected per patient and transported to the laboratory. Swabs were inoculated directly onto blood agar plates and incubated at 35°C for 24 hours before being examined. If there were specific yellow colonies, a test of catalase and coagulase using the VITEK 2 (bioMerieux Inc., Durham, NC, USA) was conducted to classify the *Staphylococcus aureus*. If the minimal inhibitory concentration of oxacillin, determined according to the national committee for clinical laboratory

standards, was ≥ 4 μg/mL, the colonies were classified as methicillin-resistant *S. aureus* (MRSA).

3.3. Ethical Considerations

The study was approved by the institutional review board at the Busan St. Mary hospital in Busan, South Korea (BSM2014-19).

3.4. Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics 21.0 (IBM Co., Armonk, NY, USA). The experimental results are presented as an arithmetic mean $\pm$ standard deviation. In the risk factor analysis, adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were obtained using multiple logistic regression analysis. Values of $P < 0.05$ were considered statistically significant.

4. Results

A total of 380 children participated: 130 in the control group and 250 in the AD group. In the control and AD groups, the mean age was 4.7 ± 4.4 years and 5.3 ± 4.7 years, respectively, with a female predominance. In the EH$^+$ and EH- groups, the mean age was 4.2 ± 4.3 years and 5.6 ± 4.7 years, respectively, and the EH$^+$ group showed a male predominance (Table 1).

The mean 25-(OH)D_3 levels and the distribution of vitamin D status in each group are shown in Table 1. There were significant differences in mean 25-(OH)D_3 levels and the distribution of vitamin D status between the control and AD groups. There were no significant differences in mean 25-(OH)D_3 levels between the EH$^+$ and EH$^-$ groups. There were significant differences in the distribution of vitamin D status between the EH$^+$ and EH$^-$ group. However, there is a seasonal variation in the sampling of 25-(OH)D_3 in each group.

There was a statistically significant difference between the EH$^+$ and EH$^-$ groups with respect to parental allergic disease history but no statistically significant difference with respect to delivery method, age of AD occurrence, or duration of AD. The difference in the mean SCORAD index severity of AD between the EH$^+$ and EH$^-$ groups was statistically significant. The distribution of clinical symptoms and the method of antiviral agent administration in the EH$^+$ group is shown in Table 2.

There were significant differences in total protein and albumin between the EH$^+$ and EH$^-$ groups. Serum IgA, IgG, IgM, and total eosinophil count levels were higher in the EH$^-$ group than in the EH$^+$ group but the differences were not statistically significant. Serum total IgE and ECP levels were higher in the EH$^+$ group than in the EH$^-$ group but the

Table 1. Comparison of Subject Characteristics[a]

	Control (n = 130)	Atopic Dermatitis				P Value[b]
		EH[+], n = 50	EH, n = 200	Total, n = 250	P Value[c]	
Male	47 (36.2)	30 (60.0)	38 (19.0)	68 (27.2)	< 0.001	0.07
Mean age, y	4.7 ± 4.4	4.2 ± 4.3	5.6 ± 4.7	5.3 ± 4.7	0.06	0.22
25-hydroxyvitamin D$_3$, ng/mL, mean ± SD	28.1 ± 11.5	25.2 ± 11.8	22.9 ± 10.4	25.0 ± 11.2	0.17	< 0.001
Vitamin D status					0.04	< 0.001
Sufficient, ≥ 30	62 (47.7)	20 (40.0)	45 (22.5)	65 (26.0)		
Insufficient, 20 - 29.9	33 (25.4)	14 (28.0)	69 (34.5)	83 (33.2)		
Deficient, < 20)	35 (26.9)	16 (32.0)	86 (43.0)	102 (40.8)		
Sampling season[d]					< 0.001	< 0.001
Spring	17 (13.1)	12 (24.0)	61 (30.5)	73 (29.2)		
Summer	42 (32.3)	25 (50.0)	49 (24.5)	74 (29.6)		
Autumn	36 (27.7)	8 (16.0)	47 (23.5)	55 (22.0)		
Winter	35 (26.9)	5 (10.0)	43 (21.5)	48 (19.2)		

Abbreviation: EH, eczema herpeticum.
[a] Values are presented as No. (%) or mean ±SD.
[b] Control group compared with atopic dermatitis group
[c] EH[+] compared with EH[-]
[d] Spring, March - May; Summer, June - August; Autumn, September - November; Winter, December - February.

differences were not statistically significant. Concerning skin cultures, there was a statistically significant difference between the two groups as *S. aureus* positive results were higher in the EH[+] group (Table 3).

Male gender was related to the presence of EH (OR, 2.56; 95% CI, 1.19 - 5.53, P = 0.01), but age and 25-(OH)D$_3$ levels were not related. The relationship between serum total IgE, ECP, and total eosinophil count levels and the presence of EH was not significant, after adjusting for age, gender, and 25-(OH)D$_3$ levels. However, the relationship between positive skin cultures and the presence of EH was significant after adjusting for age, gender, and 25-(OH)D$_3$ levels. Regarding skin cultures, after adjusting for age, gender, and 25-(OH)D$_3$ levels, the presence of MRSA was related to the presence of EH (Table 4).

5. Discussion

In this study, although there was a seasonal variation in 25-(OH)D$_3$ level sampling, we demonstrated a high prevalence of vitamin D insufficiency and deficiency in the AD group when compared with the control. Vitamin D plays a major role in innate and adaptive immunity (17, 18). In innate immunity, vitamin D deficiency causes disturbed function of cathelicidin, which may contribute to the pathogenesis of skin disease and cause AD (19). In adaptive immunity, vitamin D deficiency stimulates the induc-

tion of T regulatory cells and contributes to the development of allergic diseases (19, 20). Because of these mechanisms, many studies have been conducted to understand the inverse correlation between the severity of AD and 25-(OH)D$_3$ levels (21, 22). There is some assumption that the presence of EH may be correlated with 25-(OH)D$_3$, but there has been little research on the correlation between EH and 25-(OH)D$_3$. Recently, an EH girl whose 25-(OH)D$_3$ level was 19 ng/mL and two children with widespread EH and low serum 25-(OH)D$_3$ levels are reported (21, 23). In the present study, the EH[+] and EH[-] groups showed similar average 25-(OH)D$_3$ levels, and serum 25-(OH)D$_3$ levels were also not related to the presence of EH. However, the distribution of vitamin D status significantly differed between these two groups. Therefore, more studies about the relationship between serum 25-(OH)D$_3$ levels and the presence of EH that consider influencing factors such as sun exposure time, daily consumption of vitamin D-fortified food, and the use of sun creams are needed.

The risk factor for advancing EH is an age younger than 3 years; boys and girls are equally at risk (10). In this study, the average age, which was over 3 years, was similar between the two groups. However, boys are predominant in the EH[+] group and there is a significant correlation between the male gender and an increasing rate of EH. This finding is similar to the results of a previous study. Furthermore, EH[+] patients have been reported to have an earlier

Table 2. Comparison of the Clinical Characteristics of AD Children According to the Presence of EH[a]

Variables	EH$^+$ (n = 50)	EH$^-$ (n = 200)	P Value
Vaginal delivery	32 (64.0)	30 (60.0)	0.43
Parental allergy	25 (50.0)	131 (65.5)	0.02
Allergic rhinitis	22 (44.0)	95 (47.5)	
Contact dermatitis	4 (8.0)	66 (33.0)	
AD	3 (6.0)	5 (2.5)	
Bronchial asthma	0 (0.0)	3 (1.5)	
Age of AD onset, y	1.7 ± 2.4	2.4 ± 2.9	0.09
AD duration, y			0.59
< 1	20 (40.0)	71 (35.5)	
1 - 2	13 (26.0)	45 (22.5)	
> 2	17 (34.0)	84 (42.0)	
SCORAD index	47.6 ± 17.7	33.6 ± 18.7	< 0.001
Severity			< 0.001
Mild	0 (0.0)	37 (18.5)	
Moderate	16 (32.0)	103 (51.5)	
Severe	34 (68.0)	60 (30.0)	
Clinical symptoms	37 (74.0)		
Fever	12 (24.0)		
Systemic symptoms	13 (26.0)		
Keratoconjunctivitis	12 (24.0)		
Acyclovir treatment	50 (100)		
Intravenous	21 (42.0)		
Perioral	29 (58.0)		
Readmission	4 (8.0)		

Abbreviations: AD, atopic dermatitis; EH, eczema herpeticum; SCORAD, SCORing atopic dermatitis.
[a]Values are presented as No. (%) or mean ±SD.

onset of skin disease than EH$^-$ patients (24, 25). However, in the current study, the EH$^+$ and EH$^-$ subjects showed a similar age of onset of their underlying AD as well as their AD duration. EH$^+$ subjects have been reported to have more severe AD, similar to the results in the present study (24). The average SCORAD index of the EH$^+$ group was significantly higher and the severity of AD was significantly worse in the EH$^+$ group than in the EH$^-$ group.

AD patients with EH frequently contract secondary bacterial skin infections. Consequently, EH$^+$ subjects reported a history of cutaneous infections with *S. aureus* infections more frequently than EH$^-$ subjects. This result suggested that staphylococcal toxins increased viral replication in skin cells and that the presence of *S. aureus* colonization or infection may increase the propensity of contracting viral skin infections (26). In the current study, the development

of EH was significantly associated with MRSA, after adjusting for age, gender, and 25-(OH)D$_3$ levels, and these results are similar to those of a previous study (27). Therefore, children with AD should keep their bodies clean by bathing daily with soap or cleanser to prevent a MRSA infection which may cause the development of EH. The relationship between MRSA and the presence of EH requires more research, similar to studies of the correlation between MRSA and the severity of AD (28, 29).

High total serum IgE levels and circulating total eosinophil counts are risk factors for the development of EH and lead to a higher level of Th$_2$ polarity in their immune response (24, 30, 31). However, the current study, even after adjusting for age, gender, and 25-(OH)D$_3$ levels, the serum total IgE, ECP levels, and total eosinophil count showed no increasing trend with advancing EH.

Table 3. Comparison of the Laboratory Test Results of AD Children According to the Presence or Absence of EH[a]

Variables	EH[+] (n = 50)	EH[-] (n=200)	P Value
Total protein, g/dL	6.8 ± 0.5	7.0 ± 0.5	< 0.001
Albumin, g/dL	4.3 ± 0.3	4.5 ± 0.3	< 0.001
IgA, IU/mL	82.6 ± 69.2	96.2 ± 61.6	0.18
IgG, IU/mL	787.9 ± 237.7	846.9 ± 252.0	0.14
IgM, IU/mL	100.7 ± 43.7	113.5 ± 44.5	0.07
Total IgE, IU/mL	612.1 ± 986.0	521.4 ± 875.3	0.52
ECP, μg/L	16.5 ± 18.7	14.9 ± 17.6	0.58
Total eosinophil count, /μL	488.6 ± 435.7	494.2 ± 465.7	0.94
Positive skin culture			< 0.001
Staphylococcus aureus	34 (68.0)	87 (43.5)	
MRSA	15 (30.0)	23 (11.5)	
MSSA	19 (38.0)	64 (32.0)	
Coagulase Negative Staphylococcus	11 (22.0)	95 (47.5)	

Abbreviations: EH, eczema herpeticum, Total IgE, immunoglobulin E; ECP, eosinophil cationic protein; MRSA, methicillin-resistant *Staphylococcus aureus*, MSSA, methicillin-sensitive *Staphylococcus aureus*.
[a]Values are presented as No. (%) or mean $\pm$SD.

Table 4. Correlation Between the Risk Factors and Presence of EH[a]

Factor	OR (95% CI)	P Value
Mean age, y	1.13 (0.98-1.30)	0.08
Male gender	2.56 (1.19-5.53)	0.01
25-Hydroxyvitamin D$_3$, ng/mL	0.90 (0.96-1.03)	0.90
Total IgE, IU/mL	1.00 (0.99-1.00)c	0.41c
ECP, μg/L	1.00 (0.98-1.02)c	0.80c
Total eosinophil count, /μL	1.00 (1.00-1.01)c	0.34c
Positive skin culture		< 0.001c
MRSA	0.19 (0.04-0.92)c	0.03c
MSSA	0.42 (0.09-1.89)c	0.26c
CNS	1.54 (0.35-6.76) c	0.56c

Abbreviations: CNS, coagulase-negative Staphylococcus; ECP, eosinophil cationic protein; IgE, immunoglobulin E; MRSA, methicillin-resistant *Staphylococcus aureus*, MSSA, methicillin-sensitive *Staphylococcus aureus*.
[a]Values are presented as No. (%) or mean $\pm$SD.

Several limitations are present in the current study. Firstly, owing to its retrospective nature, the diagnosis of EH was done at the discretion of the same allergy specialist or dermatologist in a standardized manner over the course of three years. Secondly, data on recurrence and repeated episodes may have been lost if the patient moved to another hospital. In addition, we only included patients who underwent laboratory tests that included 25-(OH)D$_3$ levels. AD subjects who had no symptoms (itching, oozing, or inflammation) and had not undergone all of these tests were not included in this research. However, this study has identified certain characteristics of AD children with EH, including its features and laboratory tests with 25-(OH)D$_3$ and skin cultures.

Therefore, we conclude that male gender, positive skin culture results, and the presence of MRSA are factors influencing EH, but that serum 25-(OH)D$_3$ levels are not associated with EH in Korean AD children.

Footnote

Authors' Contribution: Kohwoon Kim: concept, drafting of the manuscript, critical revision of the manuscript. Myongsoon Sung: concept, design, critical revision of the manuscript. Junseok Kang: concept, design, acquisition of data, DATA analysis. Sung Won Kim: acquisition of data, data analysis. All authors approved the final version of the article.

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