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Clinical Significance of Atopic Dermatitis with Hypoalbuminemia in Korean Children

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Abstract

Background: Hypoalbuminemia can be a life-threatening complication of severe atopic dermatitis (AD).
Objectives: The aim of this study was to evaluate correlations between clinical features and laboratory tests of AD children with scoring atopic dermatitis (SCORAD) scores $\geq$ 40, according to the presence of hypoalbuminemia.
Methods: Children with AD between 3 and 24 months of age with SCORAD score $\geq$ 40 (n = 82), admitted to our unit from June 2007 to March 2016, were categorized to two groups of hypoalbuminemic (n = 27) and non-hypoalbuminemic (n = 55). A blood albumin level of $\leq$ 3.5 g/d on the first day of admission was considered as hypoalbuminemia. The results of clinical and laboratory tests of the two groups were evaluated and compared.
Results: Significant differences were observed in different genders, age at AD onset, and duration of AD between the groups. Compared with non-hypoalbuminemia group, significantly more patients in hypoalbuminemia group had positive test results for methicillin-resistant *Staphylococcus aureus* (MRSA) as well as allergen sensitization ($P < 0.05$). After adjusting for age and gender, male gender (odds ratio (OR) 5.962; 95% confidence interval (CI) 2.136 - 16.644, P = 0.001), positive MRSA (OR, 10.625; 95% CI, 2.823 - 39.982, $P < 0.001$) and allergen (OR, 4.622; 95% CI, 1.573 - 13.578, P = 0.005) test results were strongly related to the presence of hypoalbuminemia.
Conclusions: Hypoalbuminemia in AD children with SCORAD score $\geq$ 40 is associated with increased complications.

Keywords: Atopic dermatitis, Hypoalbuminemia, Children

1. Background

Atopic dermatitis (AD), perpetuated by gene-environmental reciprocal action, is the most common type of dermatosis in infants and children, and has the characteristics of genetic barrier defects and allergic inflammation (1, 2). The number of patients with AD is continuing to increase in many developed and developing countries (3, 4). According to the International Study of asthma and allergies in childhood (ISAAC), the prevalence of AD is 10% to 20% in children and 1% to 3% in adults worldwide (2). The lifetime prevalence of pruritus eczema in children aged 6 to 7 years has increased from 17.1% to 27.0%, while within 12 months this prevalence has increased from 13.4% to 20.6% (5, 6). Because of the increasing prevalence of AD, complications from recurrent bacterial and viral skin infections are also on the rise (7). Atopic Dermatitis complications are usually not life-threatening conditions, yet, a few associated conditions, such as hypoalbuminemia, could be dangerous to patients (8, 9).

Hypoalbuminemia is caused by epidermal permeability barrier defects in patients with AD and may occur when taking herbal medicine or restricting milk formula for AD treatment in children (10). Hypoalbuminemia is usually accompanied by hypoproteinemia and thrombocytosis. As a result, hypoalbuminemia can be a life-threatening condition owing to hypovolemic shock combined with hypoproteinemia and vascular infarction caused by thrombocytosis (11-13).

However, because hypoalbuminemia has a low prevalence, there have been only a few studies of hypoalbuminemia in children with AD.

2. Objectives

The aim of this study was to evaluate correlations between clinical features and laboratory test results of AD children with scoring atopic dermatitis (SCORAD) score of $\geq$ 40, according to the presence of hypoalbuminemia.

3. Methods

3.1. Participants

The study population consisted of patients between 3 and 24 months of age, referred to the pediatric allergy and

respiratory center at Mary's Hospital, Busan, South Korea, because of an itching sensation, dry skin, weeping, and edema. These patients were diagnosed with severe AD by allergy specialists between June 2007 and March 2016. The study was approved by the institutional review board at St. Mary's Hospital in Busan, South Korea.

Diagnosis of AD was made in accordance with the diagnostic criteria proposed by Hanifin and Rajka (14) and the SCORAD score was calculated by allergy specialists. Moderate to severe AD was defined as SCORAD score of $\geq$ 40 (15). A blood albumin level of $\leq$ 3.5 g/dL (16) on the first day of admission was considered as hypoalbuminemia. Patients with chronic or kidney diseases (bronchopulmonary dysplasia, congestive heart disease, nephrotic syndrome, etc.) were excluded from the study. Children with moderate to severe AD (n = 82) were categorized to two groups, hypoalbuminemia (n = 27) and non-hypoalbuminemia (n = 55).

3.2. Laboratory Tests

The levels of Eosinophil Cationic protein (ECP), total immunoglobulin E (IgE), and specific IgE (sIgE), as well as peripheral blood eosinophil count were assayed on the first day of admission. Levels of ECP, total IgE, and sIgE for allergens were measured using Immuno CAP 250 (Thermo Fisher, Uppsala, Sweden). A sIgE level of > 0.7 kUA/L was used to define sensiti-vity to house dust mites (Dermatophagoides pteronyssinus and Dermatophagoides farinae) and foods (eggs, milk, soybeans, and peanuts). Peripheral blood eosinophil counts were measured using an automated hematology analyzer (Coulter Counter STKS; Beckman Coulter, Fullerton, CA, USA), using blood samples collected in Ethylenediaminetetraacetic Acid (EDTA) tubes.

3.3. Skin Culture

Before AD treatment, a skin swab test was taken from 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 VITEC 2 (Biomerius Inc., Durham, NC, USA) was conducted to classify *Staphylococcus aureus*. After using VITEC 2, according to the national committee for clinical laboratory standards, the minimal inhibitory concentration (MIC) was also determined. If the MIC to oxacillin was $\geq$ 4 μg/mL, *S. aureus* colonies were classified as Methicillin-Resistant *S. aureus* (MRSA).

3.4. Statistical Analysis

All statistical analyses were performed using IBM SPSS version 21.0 (IBM Co., Armonk, NY, USA). The experiment-tal results are presented as arithmetic mean $\pm$ standard deviation. One-way analysis of variance was used for continuous variables to assess intergroup differ-ences. Multivariate logistic regression analysis was used to identify risk factors for hypoalbuminemia, and Odds Ratios (OR) and 95% Confidence Interval (CI) were calculated. Values of $P < 0.05$ were considered statistically significant.

4. Results

The clinical characteristics of both groups are shown in Table 1. Significant differences were observed in gender, average age, age at AD onset, and duration of AD between the groups. Hypoalbuminemia group was extremely male dominant, whereas non-hypoalbuminemia group had approximately equal proportion of males and females. No significant differences were observed in delivery method, average body weight, average body weight percentile, parental allergic disease history, or SCORAD score ($P > 0.05$).

The laboratory test results of both groups are shown in Table 2. Serum white blood cell and platelet counts were significantly higher in hypoalbuminemia group. Serum C-reactive protein, total protein, and albumin levels were lower in hypoalbuminemia group, yet, the difference was significant only for albumin. Serum total IgE and ECP levels, and total eosinophil counts were significantly higher in the hypoalbuminemia group ($P < 0.001$). Concerning positive skin culture results, there was no statistically significant difference between the groups ($P = 0.526$). However, the hypoalbuminemia group had a significantly higher proportion of positive MRSA results than non-hypoalbuminemia group ($P = 0.008$).

The allergy laboratory test results of both groups are shown in Table 3. The hypoalbuminemia group had a significantly higher proportion of positive test results for allergens. The hypoalbuminemia group also had a significantly higher proportion of children with multiple allergen sensitizations. The hypoalbuminemia group had a significantly higher proportion of children with milk, eggs, peanuts, soybeans, or house dust mite allergen sensitizations. Furthermore, the levels of specific IgEs to milk, eggs, peanuts, soybeans, and house dust mite were significantly higher in the hypoalbuminemia group.

The relationship between the development of hypoalbuminemia and associated factors is shown in Table 4. After adjusting for age and gender, male gender (odds ratio (OR) 5.962; 95% confidence interval (CI) 2.136 to 16.644, $P = 0.001$) and, positive MRSA (OR, 10.625; 95% CI, 2.823 to 39.982, $P < 0.001$) and allergen (OR, 4.622; 95% CI, 1.573 to 13.578, $P = 0.005$) test results were strongly related to the presence of hypoalbuminemia.

Table 1. Clinical Characteristics of the Study Groups[a]

Parameters	Hypoalbuminemia, (n = 27)	Non- hypoalbuminemia, (n = 55)	P Value
Gender, No. (%)			0.002
Male	24 (88.9)	30 (54.5)	
Female	3 (11.1)	25 (45.5)	
Age, mo	7.22 ± 2.90	10.78 ± 6.15	< 0.001
Vaginal delivery, No. (%)	16 (59.3)	32 (58.2)	0.926
Weight, kg	8.15 ± 1.57	9.35 ± 1.65	0.884
Weight percentile	40.37 ± 31.84	56.31 ± 27.51	0.467
Parental allergic disease, No. (%)	22 (81.5)	37 (67.3)	0.178
Allergic rhinitis	14 (51.9)	29 (52.7)	0.941
Atopic dermatitis	3 (11.1)	8 (14.5)	0.668
Age at AD onset, mo	4.44 ± 2.41	8.38 ± 5.34	< 0.001
Duration of AD, No. (%)			0.018
< 1 years	27 (100)	45 (81.8)	
≥ 1 years	0 (0.0)	10 (18.2)	
SCORAD score	53.73 ± 13.87	53.36 ± 10.68	0.386

Abbreviations: AD, atopic dermatitis; SCORAD, Scoring Atopic Dermatitis.
[a]Values are presented as mean ± standard deviation.

Table 2. Comparison of Laboratory Test Results Between Hypoalbuminemia and Non-Hypoalbuminemia Groups[a]

Parameters	Hypoalbuminemia, (n = 27)	Non- hypoalbuminemia, (n = 55)	P Value
White blood cell count, /mL	23,617.81 ± 6,424.56	11,131.27 ± 4,103.35	0.033
Platelet, $10^3/\mu L$	677.15 ± 206.24	395.38 ± 119.49	0.037
C-reactive protein, mg/dL	2.62 ± 6.02	2.80 ± 5.72	0.971
Total protein, g/dL	4.55 ± 0.59	6.36 ± 0.45	0.246
Albumin, g/dL	2.88 ± 0.45	4.32 ± 0.23	< 0.001
Total IgE, IU/mL	1,066.07 ± 921.04	220.71 ± 496.59	< 0.001
ECP, $\mu g/L$	121.39 ± 83.83	23.08 ± 26.86	< 0.001
Total eosinophil count, $/\mu L$	5,648.52 ± 3,616.18	784.19 ± 777.87	< 0.001
Positive skin culture, No. (%)	26 (96.2)	51 (92.7)	0.526
MRSA	11 (40.7)	8 (14.5)	0.008
MSSA	13 (48.1)	16 (29.1)	0.090

Abbreviations: ECP, Eosinophil Cationic Protein; Ige, Immunoglobulin E; MRSA, Methicillin-Resistant Staphylococcus Aureus; MSSA, Methicillin-Sensitive Staphylococcus Aureus.
[a]Values are presented as mean ± standard deviation.

5. Discussion

According to the presence of hypoalbuminemia, the data presented here shows a clear difference in clinical and laboratory test results in children with moderate to severe AD. Almost 90% of the children with hypoalbuminemia were male, and younger at the onset of AD, and had a shorter AD duration compared with the children without hypoalbuminemia. One would expect longer duration of AD in hypoalbuminemia group because of complications of allergen sensitization and increased MRAS. However, our findings that indicate hypoalbuminemia occurred mainly in male infants with AD, who were diagnosed recently, correlates with previous studies (9-13).

Almost all of the children with hypoalbuminemia in previous studies had an extremely low body weight. However, children with hypoalbuminemia in this study had almost average weight percentile, and 5 of 27 children weighed within the third percentile (9-13). Therefore, we concluded that children with normal body weight could also have hypoalbuminemia as an AD complication.

Hypoalbuminemia can occur with hypoproteinemia

Table 3. Comparison of Allergic Laboratory Test Results Between Hypoalbuminemia and Non-Hypoalbuminemia Groups[a]

Parameters	Hypoalbuminemia, (n = 27)	Non- Hypoalbuminemia, (n = 55)	P Value
Numbers of positive to allergen, No. (%)	26 (96.3)	28 (50.9)	< 0.001
Mono	1 (3.7)	8 (14.5)	
Poly	25 (92.6)	20 (36.4)	
Positive to allergen, No. (%)			
Eggs	23 (85.2)	26 (47.3)	0.001
Milk	22 (81.5)	14 (25.5)	< 0.001
Peanuts	19 (70.4)	10 (18.2)	< 0.001
Soybean	21 (77.8)	12 (21.8)	< 0.001
HDM	16 (59.3)	4 (7.3)	< 0.001
Specific IgE (kUA/L)			
Specific IgE to eggs	52.97 ± 39.65	11.54 ± 25.52	< 0.001
Specific IgE to milk	22.91 ± 32.46	3.72 ± 12.65	< 0.001
Specific IgE to peanuts	30.45 ± 35.15	3.52 ± 11.10	< 0.001
Specific IgE to soybean	28.07 ± 39.91	3.12 ± 5.15	< 0.001
Specific IgE to HDM	12.77 ± 28.39	3.76 ± 18.88	< 0.001

Abbreviations: HDM, House Dust Mite; IgE, Immunoglobulin E.
[a]Values are presented as mean ± standard deviation.

Table 4. The Relationship Between the Development of Hypoalbuminemia and Associated Factors

Variable	OR (95% CI)	P Value	aOR (95% CI)[a]	P Value
Male gender	6.667 (2.446 - 18.169)	< 0.001	5.962 (2.136 - 16.644)	0.001
Age. mo	1.142 (1.037 - 1.259)	0.007	1.129 (1.016 - 1.254)	0.024
Total IgE, IU/mL	0.998 (0.998 - 0.999)	< 0.001	0.999 (0.998 - 0.999)	0.002
ECP, μg/L	0.976 (0.967 - 0.985)	< 0.001	0.976 (0.964 - 0.987)	< 0.001
Total eosinophil count, /μL	0.999 (0.998 - 0.999)	< 0.001	0.999 (0.998 - 0.999)	< 0.001
Positive MRSA	4.727 (1.805 - 12.382)	0.002	10.625 (2.823 - 39.982)	< 0.001
Positive allergen	14.718 (3.284 - 65.964)	< 0.001	4.622 (1.573 - 13.578)	0.005

Abbreviations: aOR, Adjusted Odds Ratio; CI, Confidence Interval; ECP, Eosinophil Cationic Protein; MRSA, Methicillin-Resistant Staphylococcus Aureus; OR, Odds Ratio.
[a]Adjusted for gender and age.

(9, 11, 13). Thrombocytosis was recently described as a complication of severe childhood AD with hypoproteinemia (17-19). Hypovolemia associated with hypoproteinemia may also play a role in increased platelet counts and increase the risk of thrombosis. In other studies, an infant with severe AD and hypoalbuminemia had leukocytosis, and > 60% of the patients with hypoproteinemia also had thrombocytosis and leukocytosis (11, 17). The studies also showed that almost 90% of children with hypoalbuminemia had thrombocytosis and leukocytosis.

In a previous study, AD children with hypoalbuminemia or hypoproteinemia had high serum total IgE and eosinophil counts as well as specific IgE antibodies to food (11). In the present study, children with hypoalbuminemia had higher serum total IgE and ECP levels, and eosinophil counts than those without hypoalbuminemia. There must be more possible mechanisms by which children with moderate to severe AD with hypoalbuminemia develop elevated IgE or ECP or eosinophil count. However, due to the retrospective nature of the study we could not clarify the acting mechanisms. Therefore, more studies are needed to evaluate these mechanisms.

The children with hypoalbuminemia had very strong sensitivities to milk and eggs in this study. The presence

of food allergy or diet restriction is an important factor in evaluating the relationship among hypoalbuminemia, food allergy, and diet in children with severe AD. However, our study design was not able to provide information about presence of food allergy or diet restriction.

Concerning skin culture results, children with AD with hypoalbuminemia or without hypoalbuminemia had high numbers of cutaneous infections in this study. Children with AD have high rates of *S. aureus* infection compared with those without AD (20, 21). The two groups in this study did not have significant differences in positive skin results. However, MRSA infection that was more common in the children with hypoalbuminemia was strongly associated with the presence of hypoalbuminemia. Therefore, we assumed that MRSA infection influences skin barrier, and, as a result, hypoalbuminemia appears. More studies are needed to evaluate the relationship between AD and hypoalbuminemia, and MRSA infection.

The current study had a few limitations. Firstly, only 27 subjects with SCORAD score $\geq$ 40 with hypoalbuminemia, were between 3 and 24 months of age, which is not a large number. Hypoalbuminemia is not a common complication of AD and we included only those children, who visited the allergy center over 9 years. Therefore, we could not obtain more subjects although 27 subjects are not too small to reach objectivity. Secondly, owing to its retrospective nature, we could not obtain enough information about the presence of food allergy or diet restriction.

However, this study has identified characteristics of children with SCORAD score of $\geq$ 40 with hypoalbuminemia, including clinical features and laboratory test results. In other words, male gender, positive MRSA, and allergen are factors influencing hypoalbuminemia in Korean AD children. These findings suggest that AD in children with SCORAD score $\geq$ 40 and hypoalbuminemia is associated with increased complications.

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