Brief Report Annals of Dermatology 2022;34(4) • https://doi.org/10.5021/ad.20.249

Association of Childhood Atopic Dermatitis with Extracutaneous Infections Based on the Nationwide Cross-Sectional Study in Korea

Hee Jae Park, Mira Choi

Department of Dermatology, Ilsan Paik Hospital, Inje University College of Medicine, Goyang, Korea

Dear Editor:

As it became a pandemic era of coronavirus disease-2019, a new paradigm was necessary in the management of various chronic conditions. One of them is atopic dermatitis (AD), a chronic inflammatory skin disease, recently considered as an immune-mediated inflammatory disease[1]. AD has a lot of infectious complications due to immune dysregulation and skin barrier defects, and it has been reported that the frequency of organ involvement, such as urinary tract infection (UTI), sore throat, ear and simple skin infections, has increased[2-5]. In the case of severe AD, systemic immunosuppressants are widely used, and, as concerns over infectious diseases are recently rising, it is necessary to confirm these complications[6]. Therefore, in this study, we analyzed the association between AD and extracutaneous infections (UTI, pneumonia, otitis media, and sinusitis) in children and adolescents based on large-scale data.

Using the data from the Korea National Health and Nutrition Examination Survey (KNHNES) from 2015 to 2018, we conducted this study for 1 to 18 years old patients, divided into group with AD history and control group. This study was a population-based retrospective survey, and residential areas were divided into urban and rural. Household income per month was used in quartiles (1, low; 2, medium low; 3, medium high; 4, high). The diagnoses of AD, UTI, pneumonia, otitis media, and sinusitis were limited to cases that have been diagnosed by a doctor throughout patients' life, and the questionnaire form used for diagnosis was as follows: "Have you ever been diagnosed by a doctor with ____ (disease name)?". Since the KNHNES was collected by stratifying the population of Korean residents and selecting a group sample, statistical analysis was conducted through a complex sample data analysis method that considered weights. Participant characteristics were presented as the proportions and standard errors, and Pearson chi-squared test with Rao-Scott adjustment was used for frequency comparison in both groups. Logistic regression models were performed with infectious diseases as the dependent variable and AD as the independent variable. Multivariate models were controlled for age, sex, household income, and region. Associations between AD and the number of infections were additionally analyzed. For statistical analysis, R 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria) was used, and the cases where the p-value was less than 0.05 were defined as statistically significant. The study was approved by the institutional review board at Inje University Ilsan Paik hospital (IRB No. ISPAIK 2020-08-024).

In this study, based on the data from 2015 to 2018, a total of 5,336 (2,748 males and 2,588 females) children and adoles-

Received September 14, 2020 **Revised** December 7, 2020
Accepted December 28, 2020

Corresponding Author
Mira Choi
Department of Dermatology, Ilsan Paik Hospital, Inje University College of Medicine, 170 Juhwa-ro, Ilsanseo-gu, Goyang 10380, Korea
Tel: +82-31-910-7224
Fax: +82-31-910-7227
E-mail: mirachoi0810@gmail.com
https://orcid.org//0000-0003-2464-9675

cents, of which 712 had AD (prevalence 13.3%), were included (Supplementary Table 1). In logistic regression models, childhood AD was associated with higher odds of otitis media (odds ratio [OR] 1.28, 95% confidence interval [CI] 1.05~1.56), UTI (OR 1.66, 95% CI 1.07~2.56), and sinusitis (OR 1.46, 95% CI 1.04~2.05) but not pneumonia (OR 1.27, 95% CI 0.98~1.66) (Table 1). Childhood AD was significantly associated with one (OR 1.23, 95% CI 1.01~1.50), two (OR 1.56, 95% CI 1.13~2.14), or three infections (OR 2.22, 95% CI 1.19~4.16). As number of infections increased, the prevalence of AD trended higher (p for trend <0.01) after adjusting for confounding factors (all p<0.05) (Table 2).

These results, like previous studies, confirm that childhood AD is associated with systemic infectious diseases[2,3,5]. In a recent meta-analysis, ear infection, streptococcal pharyngitis, and UTI were all significantly increased in children and adults with AD, but no association with pneumonia was found[4]. However, since this meta-analysis was based on the data from Europe and the United States, we tried to analyze the association based on the large-scale data of Koreans and achieved similar results.

The mechanism of increased risk for extracutaneous infections in the AD has not yet been determined. Immune dysregulation represented by the type 2 inflammation, skin barrier dysfunction, decreased expression of antimicrobial peptides (AMPs), increased bacterial colonization with, for example, *Staphylococcus aureus*, and the use of systemic immunosuppressants may be related to the extracutaneous infections in AD[4]. Among these, T helper type 2 cell polarization by the type 2 inflammation promotes binding and

Table 1. Logistic regression analyses of urinary tract infection, sinusitis, otitis media, pneumonia associated with AD

Variable	Non-AD (n=4,624)		AD (n=712)		Crude OR (95% CI)	*p*-value	Adjusted OR† (95% CI)	*p*-value
	Number	%±SE	Number	%±SE				
Urinary tract infection								
No	4,485	97.21±0.37	682	95.96±0.44	1.00	-	1.00	-
Yes	139	2.79±0.37	30	4.04±0.44	1.47 (0.95~2.27)	0.084	1.66 (1.07~2.56)	0.023*
Pneumonia								
No	4,062	88.74±0.70	615	87.05±0.75	1.00	-	1.00	-
Yes	562	11.26±0.70	97	12.95±0.75	1.17 (0.90~1.52)	0.234	1.27 (0.98~1.66)	0.075
Otitis media								
No	3,357	73.80±0.98	493	70.93±1.01	1.00	-	1.00	-
Yes	1,267	26.20±0.98	219	29.07±1.01	1.15 (0.95~1.41)	0.156	1.28 (1.05~1.56)	0.016*
Sinusitis								
No	4,353	94.03±0.53	652	91.40±0.62	1.00	-	1.00	-
Yes	271	5.97±0.53	60	8.60±0.62	1.48 (1.06~2.07)	0.021	1.46 (1.04~2.05)	0.031*

AD: atopic dermatitis, SE: standard error, OR: odds ratio, CI: confidence interval. *Statistically significant (p<0.05). †Adjusted covariates: age, sex, household income, region.

Table 2. Association between AD and number of extracutaneous infections

No. of extracutaneous infections	Non-AD (n=4,624)	AD (n=712)	Crude OR (95% CI)	*p*-value	*p* for trend	Adjusted OR† (95% CI)	*p*-value	*p* for trend
0	2,845	406	-	-	0.025*	-	-	0.016*
1	1,390	222	1.13 (0.93~1.38)	0.215		1.23 (1.01~1.50)	0.039*	
2	322	68	1.39 (1.02~1.90)	0.037*		1.56 (1.13~2.14)	0.006*	
≥3	67	16	1.93 (1.05~3.54)	0.035*		2.22 (1.19~4.16)	0.013*	

Values are presented as number only. AD: atopic dermatitis, OR: odds ratio, CI: confidence interval. *Statistically significant (p<0.05). †Adjusted covariates: age, sex, household income, region.

colonization of *S. aureus* and interleukin-4 and interleukin-13 inhibit AMP production and make the body susceptible to this bacteria, thereby accelerating the inflammatory response and skin barrier damage[1,7]. In this respect, new biologics targeting the type 2 inflammation, which have been widely used recently, not only control the immune dysregulation, but also lack the immunosuppressive effect; therefore, theoretically they may be useful in preventing systemic infectious diseases due to AD, but further studies are necessary[8].

Since this report was based on a retrospective cross-sectional study using a questionnaire, it was difficult to elucidate the causal relationship, and in the process of selecting subjects, selection bias and recall bias may have occurred. In addition, since the medical records or medication information could not be verified, the severity of the infectious disease and AD was not determined, and the general health status and type of treatment of the AD patient group could not be confirmed. The possibility that the diagnosis of AD and infectious diseases may be biased by doctors was also a limitation of this study. Nevertheless, the advantage of this study is that it is a large-scale, national study, and standardization was carried out in the same way. In addition, it is meaningful as the first report in Korea on the association between AD and systemic infectious diseases in childhood using large-scale domestic data.

In conclusion, children with AD have higher odds of otitis media, UTI, and sinusitis. It is not yet known whether AD is actively treated to reduce extracutaneous infections, or whether the risk of infections increases depending on the severity of AD. Therefore, further research on the mechanism is needed to elucidate the association between AD and systemic infections. Furthermore, long-term research is necessary on how to prevent the extracutaneous infections due to AD and the effectiveness of new targeted treatments of AD which may lead to fewer skin infections.

SUPPLEMENTARY MATERIALS

Supplementary data can be found via http://anndermatol.org/src/sm/ad.20.249-s001.pdf.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

FUNDING SOURCE

None.

ORCID

Hee Jae Park, https://orcid.org/0000-0002-3998-9042
Mira Choi, https://orcid.org/0000-0003-2464-9675

REFERENCES

1. Brunner PM, Guttman-Yassky E, Leung DY. The immunology of atopic dermatitis and its reversibility with broad-spectrum and targeted therapies. J Allergy Clin Immunol 2017;139:S65-S76.
2. Narla S, Silverberg JI. Association between childhood atopic dermatitis and cutaneous, extracutaneous and systemic infections. Br J Dermatol 2018;178:1467-1468.
3. Narla S, Silverberg JI. Association between atopic dermatitis and serious cutaneous, multiorgan and systemic infections in US adults. Ann Allergy Asthma Immunol 2018;120:66-72.e11.
4. Serrano L, Patel KR, Silverberg JI. Association between atopic dermatitis and extracutaneous bacterial and mycobacterial infections: a systematic review and meta-analysis. J Am Acad Dermatol 2019;80:904-912.
5. Strom MA, Silverberg JI. Association between atopic dermatitis and extracutaneous infections in US adults. Br J Dermatol 2017;176:495-497.
6. Kim JE, Kim HJ, Lew BL, Lee KH, Hong SP, Jang YH, et al. Consensus guidelines for the treatment of atopic dermatitis in Korea (Part II): systemic treatment. Ann Dermatol 2015;27:578-592.
7. Brauweiler AM, Goleva E, Leung DYM. Th2 cytokines increase Staphylococcus aureus alpha toxin-induced keratinocyte death through the signal transducer and activator of transcription 6 (STAT6). J Invest Dermatol 2014;134:2114-2121.
8. Fleming P, Drucker AM. Risk of infection in patients with atopic dermatitis treated with dupilumab: a meta-analysis of randomized controlled trials. J Am Acad Dermatol 2018;78:62-69.e1.