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Atopic dermatitis, inhalant allergy and food allergy: A paediatric approach

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Abstract

Food and inhalant allergens have also been identified as potential trigger factors of atopic dermatitis symptoms. Here we aimed to investigate relationships between atopic dermatitis and inhalant-food allergen sensitization in Turkish children with atopic dermatitis. We included 70 patients (42 male, 28 female) with atopic dermatitis and 45 controls (30 male, 15 female) with no atopy, no atopy familial history, no atopy clinical findings no atopic dermatitis. We noted patients' and controls' age, gender, passive smoking exposure, atopy, xerosis, bath water temperature, shower gel type, clothes detergent type, blood hemoglobin, blood eosinophil count, blood eosinophil percent, values of serum immunoglobulin E, serum immunoglobulin A, serum immunoglobulin G, serum immunoglobulin M, results of inhalant allergen, and food allergen testing. We found that nine cases had inhalant allergen sensitization and 21 cases had food allergen sensitization. There were significant relationships between cases and controls in terms of count of eosinophil and percent of eosinophil ($P = .008$, $P = .009$, respectively). Humoral and cellular allergen-specific immune responses to food and inhalant allergens can be detected in patients with atopic dermatitis. Accordingly, we believe that blood eosinophil count and percent are more valuable laboratory parameters than serum total IgE for following patients with atopic dermatitis.

KEYWORDS

allergen sensitization, atopic dermatitis, food allergy, inhalant allergy

1 | INTRODUCTION

Atopic dermatitis (AD) is a chronic, inflammatory disease often manifested by intense pruritus.¹ It is characterized by cycles of exacerbations and remissions. It affects a large proportion of children and is most commonly encountered during infancy. Over the past 30 years, a 2 to 3-fold increase has been reported in pediatric AD.² The most common underlying mechanisms are immune dysregulation, impaired skin barrier integrity, genetic susceptibility, and environmental exposure.³ Although food and inhalant allergens were identified as potential triggers of AD symptoms, their exact role is

controversial.^{4,5} Herein, we aimed to investigate relationships between atopic dermatitis and inhalant and food allergen sensitization in children with AD.

2 | MATERIALS AND METHODS

This study was approved by the ethics committee of İzmir Tepecik Training and Research Hospital. Children who presented to the dermatology and pediatric allergy outpatient clinics of the same hospital between September 2019 and June 2020 and diagnosed with AD as per Hanifin and Rajka criteria constituted the study group of this prospective cohort.¹ Patients who had any other allergic conditions were

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not included. The control group consisted of healthy children who presented to the healthy children's outpatient clinic during the same period and had no personal or familial history of atopy. These patients underwent allergy tests, and all had negative test results. Parameters including age, gender, passive smoking exposure (no exposure, father is/mother is/both parents are smoking), personal history of atopy (absent/present), familial history of atopy (absent/present), xerosis (absent/present), bath water temperature (hot/warm), type of body cleansing product (made for adults/made specifically for children/solid soap) and cloth detergent type (made for adults/made specifically for children, powder soap), blood hemoglobin (Hgb) level, eosinophil count, eosinophil percentage, serum immunoglobulin E (IgE), immunoglobulin A (IgA), immunoglobulin G (IgG), immunoglobulin M (IgM) levels and inhalant, and food allergen testing results were all prospectively recorded. The inhalant allergy test was performed as a skin prick test for children older than two years old (ALK-Abello, Prick-test diagnostic, Madrid, Spain), and the food allergy test was performed as a prick-to-prick test for all children. Also, the SCORing atopic dermatitis (SCORAD) score was calculated for all patients.

2.1 | Statistical analysis

The G-Power 3.1.9.4 program (Universität Kiel, Germany) was used for statistical power analysis, which revealed that the power was 85.4%. Statistical analysis was performed by the Statistical Package for Social Sciences (SPSS Version 17.0) software (SPSS for Windows, Version 17.0. SPSS Inc. Chicago, IL, US). Variables were analyzed by Kolmogorov-Smirnov and Shapiro-Wilk tests if they were normally distributed. In the descriptive analysis, data were given as frequencies, percentages, means, and standard deviations. Pearson's chi-square test and Spearman test were used for comparing categorical data between groups. Independent samples *t* test was used for the comparison of metric and normally distributed variables. The *P*-value was considered significant when it was less than 0.05.

3 | RESULTS

The entire cohort included 70 study patients and 45 healthy controls. Study patients were aged between 2 and 13. Among these patients, 42 (60%) were male, while 28 (40%) were female. Control group consisted of 30 males (66.6%) and 15 females (33.3%). The mean SCORAD score was 22 ± 8.69 [2-39.5] for the entire cohort. Our analysis revealed no relationship between SCORAD scores and the presence of allergies ($P = .83$). Among all study participants, 7 had only inhalant allergen sensitization, 19 had only food allergen sensitization while 2 had both inhalant and food allergen sensitization, and 42 did not have an allergen sensitization. The mean SCORAD scores of the patients with inhalant allergen sensitization and food allergen sensitization were 21.92 ± 9.2 and 22.83 ± 9.19 . Our analysis elucidated that there was no significant relationship between these two groups ($P = .79$). Also, we found out that passive smoking exposure was not

associated with AD ($P = .3$). All data analysis results are displayed in Tables 1, 2, and 3.

4 | DISCUSSION

Immune dysregulation is one of the leading causes of AD.⁶ However, environmental factors including hygiene, outdoor living with contact to animals, air pollution, weather, diet, and smoking were also shown to be implicated in its pathogenesis.⁷ Tobacco smoke has several detrimental effects on both humoral and cellular immunity.⁸ In the interim, passive smoking continues to be a significant global health concern. In our study, we investigated the relationship between passive smoking exposure and AD and found that passive smoking exposure did not increase the risk of AD. Studies reported in the literature gave contradictory results regarding the association between passive smoking exposure and risk of AD: While studies conducted in South/Central America and Africa reported a significant relationship, studies reported from Asia, North America, and Europe found a less

TABLE 1 Information about allergic tendency properties of cases and controls

Parameters	Case	Control
Age	2.77 ± 2.8	3.1 ± 2.7
Gender (male/female) (%/%)	42/28 (60/40)	30/15 (66.6/33.3)
Passive smoking exposure (yes/no)	26/44	13/32
Smoking father (n)	19	9
Smoking mother (n)	3	3
Smoking father and mother (n)	4	1
Atopy (yes/no)	52/18	0/45
Him/herself	17	0
Familial	18	0
Both him/herself and familial	17	0
Xerosis (yes/no)	55/15	9/36
Bath water temperature (hot/marrow)	4/66	3/42
Shower gel type (n)	70	45
For all family	9	8
Only for children	51	32
Solid soap	10	5
Clothes detergent type (n)	70	45
For all family	31	6
Only for children	28	36
Powder soap	11	3
Inhalant allergen (positive/negative)	9/61	0/45
Food allergen (positive/negative)	21/49	0/45

TABLE 2 Complete blood count results and serum immunoglobulin levels of cases and controls

Parameters [normal range]	Case	Control	P
Passive smoking exposure: n (%)	26/70 (37.1%)	13/45 (28.9%)	0.3
Hgb [12.2-16.2 g/dL]	13.12 ± 11.6	12.53 ± 0.86	0.73
Eosinophil count (0-0.7 × 10 ⁹ /L)	0.41 ± 0.3	0.26 ± 0.27	0.008 ^a
Eosinophil percentage (0%-7%)	4.1 ± 2.9	2.7 ± 2.82	0.009 ^a
IgE [0-90 IU/mL]	176.96 ± 422.8	139.33 ± 406.56	0.6
IgA [0.7-4 g/L]	1.12 ± 3.5	2.76 ± 9.48	0.19
IgG [7-16 g/L]	6.62 ± 2.7	20.6 ± 71.3	0.19
IgM [0.4-2.3 g/L]	1.62 ± 6	2.54 ± 10.85	0.56

Note: Values are presented as means ± standard deviations.

Abbreviations: Hgb, hemoglobin; IgE, immunoglobulin E; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M.

^aP ≤ 0.05.

TABLE 3 Results of inhalant and food allergy testing of patients

Allergy tests	Cases (n/%)
Inhalant allergy	16/22.9
<i>Olea europaea</i>	1/1.4
<i>Chenopodium</i>	1/1.4
<i>Artemisia</i>	1/1.4
Grass pollens	2/2.9
<i>D. pteronyssinus</i>	3/4.3
<i>D. farinae</i>	3/4.3
Cat	2/2.9
Dog	2/2.9
<i>Parietaria</i>	1/1.4
Food allergy	55/78.4
Egg yolk	15/21.4
Egg white	15/21.4
Cow milk	10/14.3
Peanut	2/2.9
Cod fish	1/1.4
Wheat	3/4.3
Soy	1/1.4
Hazelnut	1/1.4
Almond	2/2.9
Lentil	1/1.4
Casein	1/1.4
Pear	1/1.4
Banana	1/1.4
Quince	1/1.4

significant association. Interestingly, the association between AD and passive smoking exposure was only significant in studies with a sample size of less than 5000 cases. On the other hand, studies including more than 5000 participants concluded that AD was not associated with passive smoking exposure (6.8). This finding is in line with ours. A meta-analysis that reviewed 86 studies, including 598 296 children

from 39 countries, investigated the association of active smoking, passive smoking exposure, and maternal smoking during pregnancy with childhood AD.⁹ This study concluded that childhood AD was significantly associated with passive smoking exposure. Altogether, these findings indicate that this topic is still controversial, and further research is needed.

A Th2 type of immunity leads to the production of interleukin (IL) 4, IL5, and IL13, which may locally induce IgE and eosinophilic activation and pave the way for allergic or atopic disease manifestations.¹⁰ Our study found that blood eosinophil counts and percentages of the study group patients were significantly higher than those of healthy controls. While serum total IgE levels of the former patient group were also higher than those of the latter group, the difference was statistically insignificant. Therefore, we suggest that blood eosinophil counts and percentages are more valuable parameters than serum total IgE levels in the follow-up of patients with AD. In their study, Hulshof et al. found that serum total IgE levels of the AD patients were significantly higher than healthy controls.¹⁰ However, these authors included infants only. In Seo et al. study, 572 children younger than 3 years were divided into four groups.¹¹ Children in cluster A (n = 141) had early-onset AD with high blood eosinophil counts, high serum total IgE levels, and high sensitization rates to food allergens. Children in cluster B (n = 218) had early-onset AD with low blood eosinophil counts, low serum total IgE levels, and low sensitization rates to both food and inhalant allergens. On the other hand, children in cluster C (n = 53) had early-onset AD with high C-reactive protein levels, and white blood cell counts. Children in cluster D (n = 160) had middle-onset AD with high serum total IgE and high sensitization rates to inhalant allergens. In this study, researchers suggested that this four-cluster model could be applied to children with AD who were younger than 3. Their study showed that age at onset, white blood cell and eosinophil counts, serum C reactive protein, and total IgE levels were the most important determinants in this classification.

Epidemiological and observational studies reported that inhalant allergens could trigger AD symptoms and inhalant allergy shares common inflammatory mechanisms with AD.^{4,12} It is widely accepted that sensitization to inhalant allergens occurred mostly after infancy and

increased with age.¹¹ However, literature regarding this topic is still scarce.^{4,11} In a recently published prospective clinical trial, Förster-Holst et al. reported that environmental pollen load and AD severity were correlated with each other.¹³ Accordingly, new evidence showed that grass pollen exposure might be a trigger for AD.⁴ In our cohort, 2 study patients had sensitization to grass pollens.

Celakovska et al.¹⁴ worked on 332 (120 males and 212 females) AD patients. These authors noted that 61.1% (n = 203) of their patients were sensitized to mites, 47.6% (n = 158) were sensitized to animal dander, 14.2% (n = 47) to bird feather and 24.7% (n = 82) to dust, 50.3% (167) to mixture of trees and 67.8% (225) to mixture of grasses.¹⁴ Seo et al. reported that they detected inhalant sensitization to *D. pteronyssinus*, *D. farinae*, cat dander, dog dander, cockroach, and *Alternaria* in their pediatric patients with AD.¹¹ Aktas et al. worked on children with AD, and they determined aeroallergen sensitization in 46.4% of their patients.¹⁵ These authors detected mite, pollen, and mold sensitization in 58.4%, 33.9%, and 7.5% of their AD patients. In our study, 12.9% of the patients had inhalant allergen sensitization. Five cases had sensitization to more than one inhalant allergen. Our findings indicate that whether the patient is sensitized or not is more important than the number of the aeroallergens involved, and being sensitized to even one aeroallergen poses a significant risk for AD.

Allergic diseases typically manifest in infancy, usually by development of IgE antibodies to food allergens.¹⁶ Atopic dermatitis symptoms accompany food allergen sensitization; allergic rhinitis and asthma can be added to the clinical picture at school age. This sequence is called atopic march. The prevalence of food allergen sensitization is 3% to 10% among children in developing countries.¹⁷ Also, food allergen sensitization is common in children with moderate to severe AD. Hen's egg, cow's milk, soy, and wheat account for approximately 90% of allergenic foods in children with AD.¹⁸ As per the reports published during the last decades, foods, such as, hen's eggs and cow's milk can directly activate flares of AD, particularly in sensitized infants, whereas inhaled allergens and pollen-related foods are more common triggers in older children, adolescents, and adults.¹⁹ Keck et al. analyzed baseline serum specific IgE (sIgE) to 6 foods in infants aged between 3 and 18 months with mild to severe AD with no history of food allergy.²⁰ They performed the analyses at baseline and again after three years. During follow-up, 90% of children were exposed to the previously-tested allergens, and 20% of them experienced immediate reactions to 1 or more foods such as egg, peanut, and cow milk. In another study, including children with AD aged between 1 and 3, the authors found that 4% of children were transiently sensitized at age 1.²¹ In most of these cases, there was sensitization to one food which resolved by the age of 3. Spergel et al. investigated more than 1000 infants aged between 3 and 18 months who had mild-severe AD without a history of food allergy.²² These authors observed that 16% of these infants developed one or more IgE-mediated food allergies within 3 years. Breuer et al. investigated children aged between 1 and 10 years, and they diagnosed food allergy in 64% of these children.²³ In another study conducted by Niggemann et al., 51% of all challenge tests resulted in allergic reactions, and 81% of all patients reacted to at least one allergen.²⁴

Sampson et al. found that food allergy was present in more than 60% of children with AD.²⁵

In their study, Burks et al. worked on infants who were not specifically referred with the suspicion of food allergy.²⁶ They stated that the frequency of food allergy was 30% in patients with AD. These authors also noted that children included in their study were older than those investigated in other studies.

Our study found that 21 (30%) of our patients were allergic to egg yolk, egg white, cow milk, peanut, codfish, wheat, soy, hazelnut, almond lentil, casein, pear, banana, or quince. Our literature review revealed that the mean patient age was correlated with the number of food allergen types. Since we included both infants and older children in our series, the number of food allergen types was higher than those reported in other studies.

It was suggested that there was a close relationship between AD and allergic contact dermatitis in children.²⁷ This hypothesis is based on the facts that the impaired skin barrier of children with AD can facilitate the penetration of exogenous agents and both clinical entities are associated with the mutations in the filaggrin gene. Also, it is known that atopic children are protractedly exposed to chemical substances contained in skin care products starting from an early age. This exposure increases the risk of allergic contact dermatitis in these children. Despite this fact, our analysis did not include performance of patch tests. This limitation can be considered as a weakness of our study. Our study has some other limitations, which need to be considered while evaluating its findings. First, some patients were evaluated in the dermatology outpatient clinic while others were examined in pediatric allergy units. This difference might have led to a difference in the way the study patients were approached and managed. Second, our sample size was relatively small.

Despite these weaknesses, we conclude that food and inhalant allergies can be detected in patients with AD. We suggest that a pediatric allergy specialist should examine all patients with AD regarding potential sensitization to inhalant and food allergens. It should be noted that blood eosinophil count and percentage are more valuable laboratory parameters than serum total IgE levels in children with AD.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

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REFERENCES

1. Shi K, Lio PA. Alternative treatments for atopic dermatitis: an update. *Am J Clin Dermatol*. 2019;20(2):251-266.
2. Page SS, Weston S, Loh R. Atopic dermatitis in children. *Aust Fam Physician*. 2016;45(5):293-296.
3. Malik K, Heitmiller KD, Czarnowicki T. An update on the pathophysiology of atopic dermatitis. *Dermatol Clin*. 2017;35(3):317-326.

4. Annice Heratizadeh A. Atopic Dermatitis: New evidence on the role of allergic inflammation. *Curr Opin Allergy Clin Immunol*. 2016;16(5): 458-464.
5. Robison RG, Singh AM. Controversies in Allergy: Food Testing and Dietary Avoidance in Atopic Dermatitis. *J Allergy Clin Immunol Pract*. 2019;7(1):35-39.
6. Sopori M. Effects of cigarette smoke on the immune system. *Nat Rev Immunol*. 2002;2:372-377.
7. Bonamonte D, Filoni A, Vestita M, Romita P, Foti C, Angelini G. The role of the environmental risk factors in the pathogenesis and clinical outcome of atopic dermatitis. *Biomed Res Int*. 2019;21:1-11. <https://doi.org/10.1155/2019/2450605>.
8. Kantor R, Kim A, Thyssen JP, Silverberg JI. Association of atopic dermatitis with smoking: a systematic review and meta-analysis. *J Am Acad Dermatol*. 2016;75(6):1119-1125.
9. Kantor R, Silverberg JI. Environmental risk factors and their role in the management of atopic dermatitis. *Expert Rev Clin Immunol*. 2017;13(1):15-26.
10. Hulshof L, Overbeek SA, Wyllie AL. Exploring immune development in infants with moderate to severe atopic dermatitis. *Front Immunol*. 2018;9:630.
11. Seo E, Yoon J, Jung S, Lee J, Lee BH, Yu J. Phenotypes of atopic dermatitis identified by cluster analysis in early childhood. *J Dermatol*. 2019;46(2):117-123.
12. Farinazzo E, Giuffrida R, Dianzani C, et al. What makes an inflammatory disease inflammatory? An overview of inflammatory mechanisms of allergic contact dermatitis, atopic dermatitis and psoriasis. *G Ital Dermatol Venereol*. 2020;29. <https://doi.org/10.23736/S0392-0488.20.06551-7>.
13. Förster-Holst R, Galecka J, Weissmantel S, et al. Birch pollen influence the severity of atopic eczema: prospective clinical cohort pilot study and ex vivo penetration study. *Clin Cosmet Investig Dermatol*. 2015;8: 539-548.
14. Čelakovská J, Bukač J, Ettler K, Vaneckova J, Ettlerova K. Allergy to peanuts in atopic dermatitis patients 14 year or older and the association with food hypersensitivity, inhalant allergens, asthma bronchiale and rhinitis. *Indian J Dermatol*. 2018;63(4):317-322.
15. Aktas B, Canitez Y, Sapan N. The effect of age at the time of diagnosis in atopic dermatitis on development of additional allergic disease. *Turk Ped Arş*. 2011;46:308-312.
16. Mastroianni C, Caffarelli C, Hoffmann-Sommergruber K. Food allergy and atopic dermatitis: prediction, progression and prevention. *Pediatr Allergy Immunol*. 2017;28(8):831-840.
17. Cartledge N, Chan S. Atopic dermatitis and food allergy: a paediatric approach. *Curr Pediatr Rev*. 2018;14(3):171-179.
18. Sicherer SH, Sampson HA. Food hypersensitivity and atopic dermatitis: pathophysiology, epidemiology, diagnosis, and management. *J Allergy Clin Immunol*. 1999;104:114-S122.
19. Werfel T, Breuer K. Role of food allergy in atopic dermatitis. *Curr Opin Allergy Clin Immunol*. 2004;4:379-385.
20. Keck LE, Simpson EL, Berry TM, Hanifin JM. Is food allergy testing reliable in pediatric atopic dermatitis? A population-based study. *Chem Immunol Allergy*. 2012;96:108-112.
21. Dharma C, Lefebvre DL, Tran MM, et al. Patterns of allergic sensitization and atopic dermatitis from 1 to 3 years: effects on allergic diseases. *Clin Exp Allergy*. 2018;48(1):48-59.
22. Spergel JM, Boguniewicz M, Schneider L, Hanifin JM, Paller AS, Eichenfield LF. Food allergy in infants with atopic dermatitis: limitations of food-specific IgE measurements. *Pediatrics*. 2015;136(6): e1530-e1538.
23. Breuer K, Heratizadeh A, Wulf A, et al. Late eczematous reactions to food in children with atopic dermatitis. *Clin Exp Allergy*. 2004;34: 817-824.
24. Niggemann B, Sielaff B, Beyer K, et al. Outcome of double-blind, placebo-controlled food challenge tests in 107 children with atopic dermatitis. *Clin Exp Allergy*. 1999;29:91-96.
25. Sampson HA, Albergo R. Comparison of results of skin tests, RAST, and double-blind, placebo controlled food challenges in atopic dermatitis. *J Allergy Clin Immunol*. 1984;74:26-33.
26. Burks AW, Mallory SB, Williams LW, Shirrel MA. Atopic dermatitis: clinical relevance of food hypersensitivity reactions. *J Pediatr*. 1988; 113:447-451.
27. Romita P, Foti C, Stingeni L, et al. Contact Allergy in Children with Atopic Dermatitis: A Retrospective Study. *Endocr Metab Immune Disord Drug Targets*. 2019;19(7):1083-1087. <https://doi.org/10.2174/1871530319666190211123342>.

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