

Clinical Features and Immunological Markers of Atopic Dermatitis in Elderly Patients

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Key Words

Atopic dermatitis • Aging • *Staphylococcus aureus*

Abstract

Background: Atopic dermatitis (AD) is increasing among the elderly. *Staphylococcus aureus* colonization is one of the most important aggravating factors in AD. **Objective:** This study analyses the clinical features of AD in elderly patients and determines the pathogenic roles of staphylococcal superantigens in AD with low and high total IgE levels. **Methods:** *S. aureus* enterotoxin genes were evaluated using PCR. Additionally, *S. aureus*-specific IgE levels and peripheral blood lymphocyte profiles were assessed. **Results:** A total of 44 women and 77 men diagnosed with AD with a mean age of 68.92 ± 6.51 years were evaluated. In 17 (68%) patients with AD and low levels of total IgE, there was a positive correlation between the positive results for enterotoxin B, *S. aureus*-specific IgE antibodies and Th1 cytokine profiles (Spearman's rank correlation test, $r = 0.89$, $p < 0.05$). **Conclusion:** Our results indicate that AD patients with low total IgE levels differ in immunopathogenesis from AD patients with high circulating levels of total IgE AD.

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Introduction

Atopic dermatitis (AD) is a common skin disorder that affects approximately 15–25% of children during early childhood. AD is much less common in adults, especially in the elderly. The prevalence of AD in patients who are 50 years of age or older is estimated to range from 1.5 to 10%; however, different forms of dermatitis exist and some may be caused by IgE reactions [1–4].

Most elderly patients with AD have had this disorder since childhood; only limited clinical and immunological analyses are available regarding cases of adult-onset AD [1, 2, 5, 6]. Based on the literature and our observations of elderly AD patients, the incidence of AD clinical manifestations that persist or first appear during adolescence and subsequent late adulthood has increased. The frequency of atopic disease has gradually increased among the elderly; however, bronchial asthma, allergic rhinoconjunctivitis and especially AD are underdiagnosed and undertreated in this population.

Allergic reactions are most likely also associated with the changes in the immune system that accompany aging in elderly patients. In older people, it is possible to observe a domination of the Th2 profile, changes in lymphocyte cell populations (decreases in CD8 and increases in CD4

levels) and changes in circulating antibody concentrations. The prevalence of Th2 profile among elderly individuals has already been extensively investigated [5, 6].

AD can be categorized as either extrinsic or intrinsic. Patients with extrinsic AD demonstrate high total serum IgE levels and the presence of IgE antibodies specific for environmental and food allergens, whereas patients with intrinsic AD exhibit normal total IgE levels and an absence of allergen-specific IgE antibodies. Clinically, intrinsic AD has a relatively late onset, and it is more common in elderly patients [7, 8].

This study analyses the clinical features of AD in elderly patients. Further, the pathogenic role of staphylococcal superantigens in patients with AD is also examined.

Methods

Patients

A total of 6,511 subjects aged 60 years or older (mean age 69.3 ± 18.2) were prescreened for potential cases of AD based on typical skin changes and a positive history of AD. The study included 3,870 women and 2,641 men who had visited one of 16 allergy and geriatric outpatient clinics or dermatology units in Poland. A positive medical history confirmed by Hanifin and Rajka criteria combined with a dermatological examination was used for AD diagnosis. In questionable cases of AD diagnosis, histopathological examinations of lesion skin were used for confirmation. However, skin biopsies were carried out in the majority of patients. Of the prescreened patients, 121 (1.86%) were diagnosed with AD and were included in this study. A control group of 106 subjects (mean age 68.1 ± 15.9 years) that did not have AD or other atopic diseases was also established.

Clinical manifestations of AD were evaluated by dermatological and allergological examination. Skin biopsy specimens were obtained from chronic eczema skin lesions. Giemsa and hematoxylin-eosin stainings were carried out to evaluate routine histopathological findings. Patients with other dermatological complaints or systemic diseases that involved the skin were carefully excluded.

The Isolation and Identification of *Staphylococcus aureus*

Skin swabs were taken from the lesions of AD patients and the skin healthy control subjects using sterile swabs. The samples were inoculated onto blood agar plates (Bioconnections) and incubated for 48 h at 37°C . *S. aureus* isolates were identified by Gram staining that displayed Gram-positive cocci; further, colonies were negative for catalase and positive for coagulase. Established *S. aureus* colonies were further processed, and enterotoxin genes were evaluated using PCR. DNA was extracted using a Magna Pure Compact Nucleic Acid Isolation Kit in combination with an automated Magna Pure Compact Instrument (Roche). PCR amplification of toxin genes was carried out using a UNO thermocycler (Biometra). Cycling conditions were as follows: 92°C for 6 min, followed by 45 cycles of 96°C for 4 min, 58°C for 3 min and 81°C for 1 min. The following toxin genes were examined: SEA, SEB, SEC, SED and TSST. The sequences of staphylo-

Table 1. Sequences of the staphylococcal enterotoxin-specific oligonucleotide primers

Genotype	Primer	Oligonucleotide sequence 5' → 3'
sea	SEA1	TTGGATCAAAACGGTACCAA
	SEA 2	GACTTAAAACCTATTGGACG
seb	SEB 1	TCGGCTTTAATCTGTTGAAA
	SEB2	GAAATCGGTCTCCCAAATGA
sec	SEC 1	AATGGTCTTGAAAATGGGTA
	SEC 2	CTGGAGAAATCTTAGGTAAT
sed	SEC1	ATTGGTCTGAATGGACCTT
	SEC2	AAAAATCTGCTAAGCTGCCA
tst	TSST 1	ACTAAATGGTGCCCTACTAA
	TSST 2	TCCTATGAGGTCTGGAAATC

Table 2. Characteristics of the elderly patients with AD who were included in this study

Clinical features of AD	
Men	77 (63.6%)
Positive history of atopy	73 (60.9%)
Current smokers	26 (21.6%)
Former smokers	42 (34.7%)
Mean AD duration, years	48.12 ± 23.8
Mean age of AD onset, years	16.11 ± 12.41
Four positive criteria according to Hanifin and Rajka	81 (67%)
Three positive criteria according to Hanifin and Rajka	40 (33%)
Mean SCORAD score	32.19 ± 12.90
A presence of atopic asthma	14 (11.5%)
A presence of allergic rhinitis	42 (34.6%)
A presence of allergic rhinitis and asthma	6 (5.2%)

coccal toxin-specific oligonucleotide primers are presented in table 1. PCR products were examined by 1.6% agarose electrophoresis, and bands were visualized with ethidium bromide.

Allergy Testing Procedures

Skin prick tests were carried out with inhalant (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, grass pollen, birch, hazel, alder, mugwort, *Alternaria*, *Cladosporium*, *Aspergillus*, cat, dog, cockroach and storage mites) and food (cow milk, egg, wheat, corn, tomato, potato, orange, apple, cocoa, celery, fish mix, and nut mix) allergens. All patients were examined to evaluate their total IgE and antigen-specific IgE (sIgE) antibody serum levels in response to the aforementioned skin test allergens. Allergen levels were determined using the ELISA CAP system (Pharmacia). Additionally, IgE antibodies specific for *S. aureus* staphylococcal enterotoxin A, m80, staphylococcal enterotoxin B, m81, staphylococcal enterotoxin C, m223, staphylococcal D enterotoxin, m224, and staphylococcal enterotoxin TSST, m226, were eval-

Table 3. Clinical comparison of elderly patients with AD with low and high total IgE

	AD with high total IgE	AD with low total IgE	p
Number of patients	96 (79%)	25 (21%)	0.0023 ¹
Men	63 (52%)	14 (56%)	NS
Mean SCORAD	34.09 ± 12.98	30.11 ± 23.56	NS
Four positive criteria according to Hanifin and Rajka	64 (66.7%)	16 (64%)	NS
Mean total IgE, IU/ml	2,540.31 ± 2,233.91	53.91 ± 24.91	0.0008
Mean time of AD duration, years	48.11 ± 18.89	41.67 ± 17.56	0.02
Mean age at which AD started, years	3.98 ± 2.56	6.56 ± 4.81	0.01

NS = Not significant. p for χ^2 test.

¹ p for Student's t test.

uated using a Pharmacia CAP assay (Pharmacia) according to the manufacturer's instructions.

Immunological Analyses

Blood lymphocyte profiles were measured via the whole-blood method using fresh 10-ml EDTA blood samples according to Machura et al. [9]. The following lymphocyte markers were measured using ImmunoGEN kits (BD Bioscience) and a FACSCanto II flow cytometer (Becton Dickinson): CD3, CD29, CD1656, CD4, CD8 and HLADR. To assess the Th1/Th2 profile of patients, concentrations of IL-2, IL-4, IL-5, IL-10, TNF- α and IFN- γ in blood were measured using a human Th1/Th2 cytokine kit II (ImmunoGEN); samples were run on a FACSCanto II. Cytokine concentrations are presented in pg/ml. Measurement sensitivities were as follows: for IL-2 > 31.2 pg/ml; IL-4 > 10 pg/ml; IL-5 > 5.1 pg/ml; IL-10 > 11.6 pg/ml; IL-13 > 13.6 pg/ml; TNF- α > 6.5 pg/ml; IFN- γ > 5.2 pg/ml.

Statistical Analyses

Nonparametric statistical analyses were performed using the χ^2 test and the Mann-Whitney U test. Spearman's rank correlation test was used to examine any possible trends. Statistics, version 8.0, (StatSoft) was used for all statistical analyses; a p value of <0.05 was considered to be statistically significant after Bonferroni correction.

Results

This study included 121 patients (44 women and 77 men) diagnosed with AD with a mean age of 68.92 ± 6.51 . Patient characteristics are summarized in table 2. Typical childhood AD with geriatric recurrence was observed in approximately 67% of patients; geriatric onset of AD was observed in 21% of patients and 12% of patients exhibited adult onset of AD. Chronic, atopic eczema was confirmed by skin biopsy in 104 (85.9%) patients. In the remaining patients, the biopsies revealed nonspecific results. Mastocytosis was noted in 4 cases.

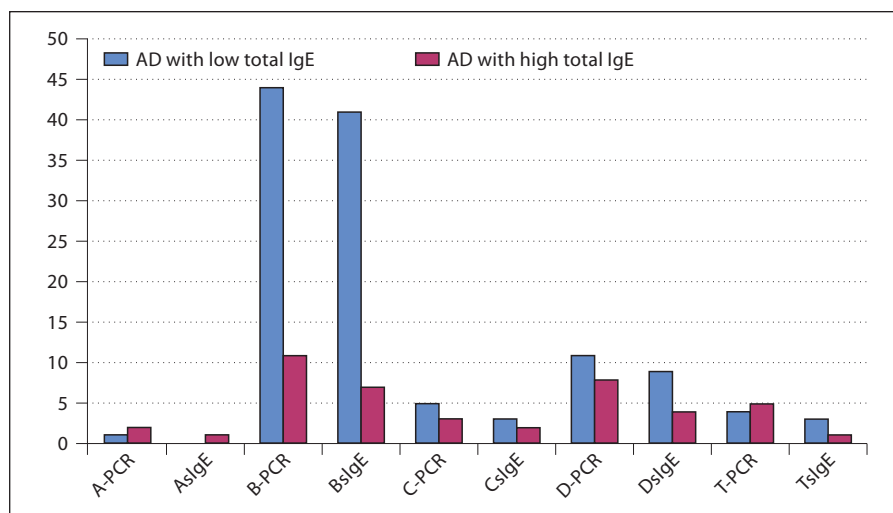
Skin manifestations were predominantly observed on the extensor sites of the upper extremities (85.9% of patients), neck (78.4%), lower extremities (76.9%) and face (56.9%). Significant lichenification was localized to the extremities and neck in 56% of patients. Concomitant contact dermatitis was observed in 28 (23%) patients; of these, 23 subjects exhibited sensitization to nickel. In 25 (21%) cases, allergy diagnosis was negative and AD with low total IgE was confirmed; these patients were placed into group B. The remaining 96 (79%) patients tested positive for allergies and were placed into group A. The mean total IgE level for group A patients was $2,540.3 \pm 3,233.9$ IU/ml; values ranged from 3.3 to 21,230.5 IU/ml. *D. pteronyssinus* and *D. farinae* were the most predominant allergens, with 72 and 70.9% of patients being allergic to them, respectively. Grass (68.4%), birch (45.9%), *Alternaria* (43.7%) and cow milk (25.6%) allergens were the most frequent positive in skin prick tests and/or specific IgE evaluations. Clinical comparisons between groups A and B are presented in table 3.

S. aureus was isolated from 65 (68%) patients in group A and 23 (92%) in group B. In the control group, only 41 (38.6%) subjects were positive for *S. aureus* (p = 0.012).

S. aureus isolates were positive for enterotoxin genes in 47 (49.5%) patients in group A, 20 (80%) in group B and 5 (4.7%) in healthy subjects (p = 0.024). There were differences regarding the types of enterotoxins present in isolates from the different patient groups and the control group; in general, enterotoxins B and D were the most common.

The cutoff value of *S. aureus* enterotoxin-specific IgEs was ≥ 0.35 IU/ml. The positive predictive value of enterotoxin-specific IgE was observed in 28 (29.2%) patients in group A, 19 (76%) patients in group B and 1 (1%) healthy

Fig. 1. PCR detection of *S. aureus* enterotoxins and the corresponding specific IgE in patients with AD. Percentages of patients ($n = 67$) for whom PCR revealed positivity to enterotoxin A (A-PCR: $n_1 = 3$), enterotoxin B (B-PCR: $n_2 = 56$), enterotoxin C (C-PCR: $n_3 = 8$), enterotoxin D (D-PCR: $n_4 = 29$) and enterotoxin TSST (T-PCR: $n_5 = 5$), and who had elevated specific IgEs ($r = 47$) for the enterotoxin A (AsIgE, $r_1 = 1$ patient), enterotoxin B (BsIgE, $r_2 = 48$), enterotoxin C (CsIgE, $r_3 = 8$), enterotoxin D (DsIgE, $r_4 = 13$) and enterotoxin TSST (TsIgE, $r_5 = 4$).



person ($p = 0.021$). Positive PCR *S. aureus* enterotoxin detection results were correlated with enterotoxin-specific IgE in all examined groups according to Spearman's rank correlation test ($r = 0.74$, $p < 0.05$). Detailed data are presented in figure 1. Blood lymphocyte profiles are presented in table 4.

The characteristics of blood lymphocytes profile among healthy elderly individuals were comparable to patients with AD alone (group A). A dominant Th2 profile was observed in 87 (92%) patients in group A and in 89 (84%) of the control individuals tested. A Th1 profile was observed in 21 (84%) patients in group B. Cytokine concentrations are presented in figure 2.

Seventeen (68%) patients with AD and low total IgE (group B) exhibited a positive correlation between PCR positivity for enterotoxin B, *S. aureus*-specific IgE antibodies, and a dominant Th1 profile according to the Spearman rank test ($r = 0.89$, $p < 0.05$). Similar correlation was not found in AD patients with high level of total IgE (group A).

Discussion

Similar to other atopic diseases, the incidence of AD is gradually increasing in countries with aging populations [3–5]. The prevalence of AD in our 6,511 analyzed subjects was 1.86%, which agrees with other published data [3, 4].

The dermatological and allergological features of AD in our elderly patients were similar to those of adult AD patients [1, 2, 5]. A positive history of atopy, meeting the

Table 4. Blood lymphocyte profile among patients with two types of AD: a comparison

Phenotype of lymphocyte	AD with high IgE, %	AD with low IgE, %	p χ^2 test
CD3+	68.7	67.1	NS
CD19+	12.1	11.7	NS
CD16+CD8+	8.1	9.3	NS
CD4+	49.2	38.4	0.045
CD8+	17.5	22.2	0.032
CD3+HLA DR	4.6	5.3	NS
CD4/CD8	2.2	1.1	0.041

Hanifin and Rajka criteria as well as skin lesions were typical, as has been observed in younger patients with AD. These results support the observations reported by Tanei and Katsuoka [1].

D. pteronyssinus and *D. farinae* were the most common positive allergens in the skin prick test and the allergen-specific IgE assays. These results are consistent with other AD studies in elderly patients [1, 10, 11]. These findings suggest that allergy diagnostics should be performed in elderly patients; however, skin prick tests may not always be reliable when performed on aging skin. On the other hand, we observed contact dermatitis more often in elderly patients with AD compared to values reported in the literature [1, 12, 13]. Our findings confirmed that 21% of elderly patients had AD with low total IgE and were not allergic to common allergens. These values are slightly higher than those of other reports (5–15%), which have investigated younger populations [9, 14, 15]. It is possible

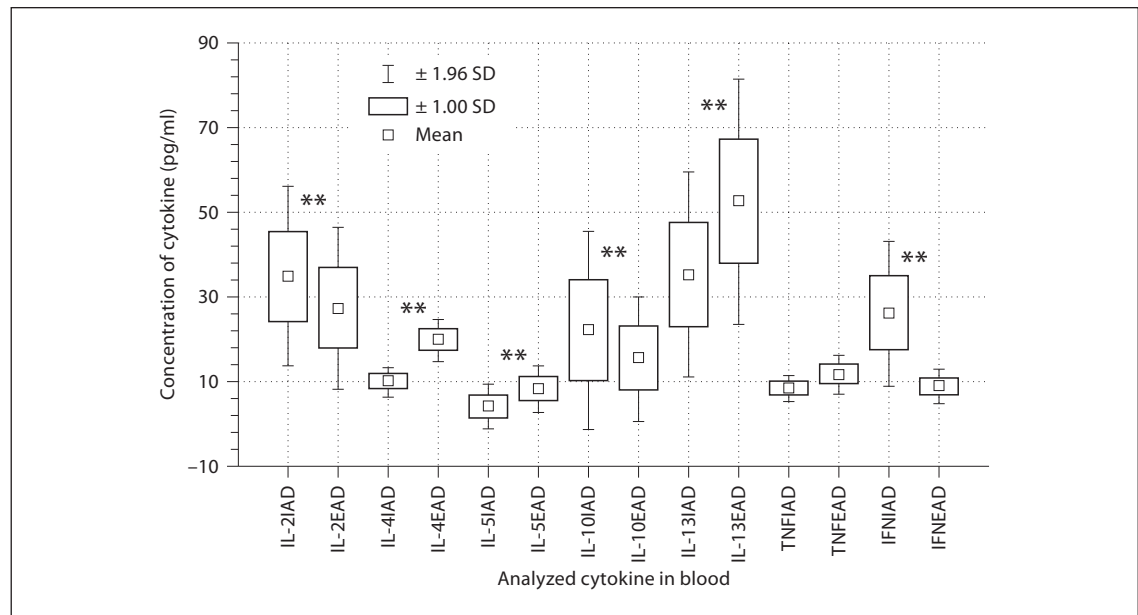


Fig. 2. Blood concentrations of cytokine in patients with high total IgE and low IgE. ** Statistically significant, Mann-Whitney U test, $p < 0.05$ with Bonferroni correction. IL-2IAD = mean blood concentration of interleukin 2 in AD with low total IgE, IL-2EAD = mean blood concentration of interleukin 2 in AD with high total IgE, IL-4IAD = mean blood concentration of interleukin 4 in AD with low total IgE, IL-4EAD = mean blood concentration of interleukin 4 in AD with high total IgE, IL-5IAD = mean blood concentration of interleukin 5 in AD with low total IgE, IL-5EAD = mean blood concentration of interleukin 5 in AD with high total IgE, IL-10IAD = mean blood

concentration of interleukin 10 in AD with low total IgE, IL-10EAD = mean blood concentration of interleukin 10 in AD with high total IgE, IL-13EAD = mean blood concentration of interleukin 13 in AD with low total IgE, IL-13IAD = mean blood concentration of interleukin 13 in AD with high total IgE, TNFIAD = mean blood concentration of tumor necrosis factor in AD with low total IgE, TNFEAD = mean blood concentration of tumor necrosis factor in AD with high total IgE, IFNIAD = mean blood concentration of interferon gamma in AD with low total IgE, and IFNEAD = mean blood concentration of interferon gamma in AD with high total IgE.

that AD with low total IgE is more prevalent in elderly AD patients. However, the presence of IgE antibodies specific to staphylococcal antigens could exclude the confirmation of intrinsic AD. It could indicate that some patients with a preliminary diagnosis of intrinsic AD should have their diagnosis changed.

Clinically, AD patients with low total IgE compared to AD patients with high total IgE exhibited a later onset of AD, milder disease severity and a lack of IgE antibodies specific to common allergens; further, these patients were predominately women. These differences have been previously reported in younger populations [14, 15].

The colonization of *S. aureus* on the skin plays an important part in the pathology of AD [16–19]. Various staphylococcal superantigens have been analyzed for their potential to intensify AD or other skin diseases [16, 20, 21]. Previous studies have shown that staphylococcal enterotoxins A, B, C, D, E and TSST are immunopathological agents that can induce inflammation in AD [17–20]. How-

ever, no clear data exist identifying which enterotoxin is most immunostimulatory. The authors concentrated on superantigens for which IgE measurements are available. Interestingly, the manifestation of staphylococcal superantigens differed in the two forms of AD in our study. A predominance of enterotoxins B and D was observed in *S. aureus* isolates from AD patients with low total IgE. This correlated with the presence of enterotoxin B- and D-specific IgE antibodies. Such clear differences in *S. aureus* phenotypes in both types of AD have not been previously observed. Kim et al. [21] reported the presence of staphylococcal enterotoxins in intrinsic and extrinsic AD. On the other hand, evidence has shown that serum levels of staphylococcal enterotoxin A- and B-specific IgE antibodies are elevated in children with atopic (extrinsic) AD [22]. The correlation between the types of AD, total IgE and superantigen-specific IgE was not clear in previous studies, and sensitization to enterotoxins could not be differentiated between extrinsic intrinsic forms of AD [23, 24].

Immunological data suggest that AD with low total IgE is characterized by the prevalence of CD8+ lymphocytes and a dominant Th1 profile. Moreover, AD with low total IgE was correlated with the presence of staphylococcal enterotoxins B and D as well as enterotoxin-specific IgE antibodies. These immunological observations could distinguish AD with low total IgE from AD with high total IgE, but as mentioned above, there is no evidence that AD with low total IgE is consistent with intrinsic AD in this study.

The observed low concentrations of IL-4, IL-5 and IL-13 as well as the higher expression of IFN- γ in our elderly patients with AD and low total IgE were comparable to nonatopic or intrinsic AD patients [25]. Our data suggest that patients with AD and low total IgE are not sensitized to typical protein allergens that induce Th2 responses, instead, they are sensitized to staphylococcal superantigens that induce Th1 responses. However, several reports suggest that sensitization to staphylococcal superantigens could induce a Th2 or a mixed Th1-Th2 response [17–19]. Perhaps, the existence of high IL-10 concentrations typical to Th2 responses could be evidence that there are Th1/Th2 responses in patients with staphylococcal superantigen manifestations. Topical superanti-

gen exposure has been observed to induce an epidermal accumulation of CD8+ T cells and a mixed Th2/Th1 type dermatitis in chronic atopic skin inflammation [18].

In elderly patients with AD and low serum IgE, the presence and activity of staphylococcal superantigens could be enhanced by favorable conditions created by an appropriate cytokine profile. The role of *S. aureus*-specific IgE antibodies in AD requires further investigation.

Conclusion

Our findings suggest that AD in elderly patients has clinical features that are similar to those observed in younger patients. In elderly patients, the immunopathogenesis of AD with low total IgE appears to be markedly different; this is likely due to the Th1 and/or Th2 response to staphylococcal enterotoxin superantigens.

Acknowledgment

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