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INVESTIGATIVE REPORT

High Serum Total IgE Predicts Poor Long-term Outcome in Atopic Dermatitis

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Most patients with severe atopic dermatitis have elevated serum IgE levels, but there has been little research into IgE as a predictive biomarker in long-term disease outcome. The aim of this study was to evaluate the predictive value of IgE and other factors in patients with atopic dermatitis in a university clinic setting. There were 169 eligible patients (14–78 years) with a mean follow-up of 4.15 years. High baseline IgE (≥10,000 IU/ml) was the most important patient-related factor for a poor long-term outcome, being negatively associated with good treatment response (odds ratio (OR) 0.062, $p = 0.002$). Only 14.3% of patients with this high baseline IgE achieved a good treatment response in follow-up, compared with 79.7% in patients with lower (<1,000 IU/ml) IgE values ($p < 0.001$). Serum total IgE may provide an easily measurable way to predict long-term outcome, and to help to select those patients in need of closer follow-up. ***Key words: atopic dermatitis; immunoglobulin E; biomarker; treatment response.***

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Atopic dermatitis (AD) is a chronic, relapsing, and intensely pruritic inflammatory skin disease and one of the most frequent inflammatory skin diseases (1, 2). Patients with AD often have comorbidities, including food allergies, asthma and allergic rhinoconjunctivitis (3–5). The pathogenesis of AD is complex, including epidermal barrier dysfunction and immunological events, both of which contribute to the inflammatory condition of the skin (6, 7). In AD the clinical phenotype may be the result of many distinct genetic variations interacting with numerous environmental factors (2, 3). In particular, there is a strong association between filaggrin (*FLG*) gene loss-of-function mutations and AD; approximately 30% of patients with AD have a loss-of function mutation in the *FLG* gene (8–10).

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention (7). Objectively measurable biomarkers would present a valuable tool in AD. These biomarkers may help with the choice of treatment regimen, in the prediction of treatment response, and may provide information on disease progression. *FLG* mutations have been suggested as a possible biomarker in AD (2, 11). Other proposed possible biomarkers include serum levels of CD30, macrophage-derived chemokine (MDC), interleukins 12, 16, 18 and 31, and thymus and activation-regulated chemokine (TARC), serum eosinophil cationic protein (ECP), total eosinophil count, and T helper 2 cell cytokines CCL17, CCL22, CCL27 (12–17). Serum total IgE is another possible biomarker: most AD patients with severe disease have elevated total IgE levels and recent studies have shown a significant correlation between decreased disease activity, including normalization of Th2 polarity, and a decrease in total IgE levels during follow-up (18–21). There has been little research into the use of total IgE as a predictive biomarker for long-term outcome in AD.

The primary aim of this study was to examine the use of a possible biomarker – serum total IgE – and other patient- or treatment-related factors as outcome-predicting factors of long-term treatment response in AD. We investigated associations between baseline IgE values and the change in IgE levels during follow-up, and the clinical course of AD and treatment response on maintenance-type topical treatment. We also analysed other patient- and treatment-related factors in relation to the treatment results in order to evaluate factors associated with long-term outcome and possible risk factors for a poor outcome

MATERIAL AND METHODS

This study is part of an ongoing AD genetics study in Finnish patients, which started on 1 June 2011. This is a retrospective study with follow-up data prior to the baseline of the aforementioned AD genetics study. The baseline for this study was the first visit of study subjects to the specialized AD clinic at the Skin and Allergy Hospital of Helsinki University Central Hospital, a referral centre for dermatology and allergology. The endpoint was the enrolment visit for the AD genetics study. The study participants are patients with AD referred to the specialized AD clinic by general practitioners or dermatologists due to difficulties in obtaining adequate treatment results or the severity of their disease. The study was approved by the local ethics committee.

Data prior to the AD genetics study were gathered from all eligible subjects. Patients with less than one year of follow-up

and patients ≤13 years of age were excluded. In total, data from 169 patients were eligible for analysis. Data were collected from electronic patient records from January 1, 2002 onwards. Baseline information on IgE levels (measured using CAP system-specific IgE fluorometric enzyme immunocapture assay), clinical AD severity, previous and/or concomitant medications and other relevant information was collected. Clinical severity of AD at baseline was obtained from patient charts based on a clinical examination by a dermatologist. Patients were divided into 3 groups based on clinical severity: mild (investigator's global assessment (IGA) 1–2), moderate (IGA 3) and severe (IGA 4–5).

Patients enrolled in the AD genetics study were interviewed and examined by a dermatologist. The data from interviews were confirmed from patient records when necessary and applicable. Data were collected on demographic factors, atopic manifestations in close relatives, other manifestations of atopy (rhinitis, conjunctivitis, asthma, food allergy), current and past treatment regimens on AD, current medications, history of oral medications used for AD, hospitalization because of AD, age of onset, smoking (prior and current), skin-prick testing, patch-test diagnosed contact allergies, and history of herpes simplex virus (HSV) infections. Clinical symptoms were assessed and graded again by a dermatologist. Symptoms of atopic hand and/or palmar eczema were assessed separately. The data gathered from these interviews and clinical examinations were used as a primary source for endpoint data.

Treatment response was evaluated at the endpoint. "Complete remission" was defined as the absence of AD symptoms in previously symptomatic patients, and "good response" was defined as alleviation of symptoms at the endpoint compared with baseline, grading of dermatitis being mild or clear at the endpoint. Adherence to treatment was also assessed on a scale of 1–3 (poor, average, good), based on how well the patient had been following the maintenance treatment regimen.

Topical treatments for patients in this study were either maintenance treatment with topical tacrolimus or maintenance treatment with either a combination of topical tacrolimus and topical corticosteroids, or topical corticosteroids alone. Patients were visiting a specialized AD clinic and had received a long-term treatment plan from a dermatologist. They also received hands-on training for adequate topical therapy regimens from a nurse, when necessary. In some cases the treatment was initiated with a few daily appointments with a nurse to strengthen adherence.

Statistical analyses were performed to identify factors associated with, or predictive for, both a good treatment response and complete remission. Univariate and adjusted odds ratios (OR) with 95% confidence intervals (95% CI) were calculated using logistic regression models. Factors indicating an association (p-value ≤0.10) in the univariate analyses were included as covariates in the multivariate analysis for adjusted ORs. The variables eligible for the multivariate logistic regression model were tested for significant interactions. The non-parametric Wilcoxon signed-rank test was used to calculate p-values for the changes in total IgE and the clinical severity of AD between the baseline and the end of follow-up. Studies on analyses performed with immunological data, such as IgE and interleukin 4, have shown that these markers tend to have a positively skewed distribution. Conducting analyses with data transformed to a logarithmic scale has been shown to illustrate a better measure of central tendency, as data analysed with a logarithmic scale are less subjected to distortion by the unusually large values in the tail of the positively skewed distribution of the data (22). Based on this information, IgE values were analysed with the logarithmic scale. All statistical analyses were performed using SPSS 21 and SPSS 22 for Mac (IBM, Chicago, IL, USA).

RESULTS

Patients and serum total IgE

There were 169 eligible patients (age range 14.0–78.1 years (mean 33.0 years); 59% women, 41% men). Mean follow-up time was 4.15 years (range 1.0–10.4 years). Most of the subjects had a strong atopic diathesis with high levels of allergic rhinitis, allergic conjunctivitis, food allergies, and asthma, and high IgE values (median 1,501 at baseline) (Table I).

At baseline, 71.0% of patients had moderate–severe AD symptoms. By the end of follow-up this proportion had decreased to 29.7%. The proportion of patients with clear-mild symptoms was 29.0% at baseline and increased to 70.2% ($p<0.001$) during follow-up.

Median total IgE values were 1,501 IU/ml (mean 5,670 IU/ml) at baseline and 1,130 IU/ml (mean 5,121 IU/ml) at end of follow-up ($p<0.001$). Seventy-nine percent of patients with good adherence had good response or total clearance vs. 53% of patients with worse adherence ($p=0.05$). Assessed adherence was associated with the IgE response: 45% of patients with good adherence had a significant (>50%) IgE decrease vs. 25% of patients with poor adherence ($p=0.02$).

Factors associated with long-term outcome

Predictive factors for a good treatment response and for complete remission were assessed separately. Sex, symptoms of allergic rhinitis or conjunctivitis, food allergy, hand eczema (neither dorsal or palmar), any positive reactions in skin-prick testing, prick-test positivity for peanuts, a positive history of HSV infection, systemic immunosuppressive medication for indications other than AD, current smoking or a history of smoking, age of onset, main topical therapy used, and regular use of oral antihistamines/montelukast showed no associations with either a good treatment response or a total remission in univariate analysis. Younger age and milder clinical baseline severity showed an association with a good treatment response, but not with complete remission. Asthma, baseline total IgE, and the presence of patch-test diagnosed contact allergies were negatively associated with both a good treatment response and a complete remission of AD symptoms in univariate analyses.

After adjusting the multivariate analyses, the presence of contact allergies and high baseline IgE values ≥10,000 IU/ml remained risk factors for a poor long-term outcome and were statistically significantly negatively associated with a good treatment response (OR 0.162 and 0.062, respectively), and with complete remission (OR 0.287 and 0.158, respectively) (Table II). Only 16.5% of patients with diagnosed contact allergies achieved complete remission and 34.5% showed a good treatment response. In patients without contact allergies the proportions were vs. 45.4% and 71.3%, respectively. In patients with baseline IgE ≥10,000 IU/ml proportions achieving complete

Table I. *Patient demographics and other variables*

Variable	*n* (%)
Age, baseline	
0–20 years	37 (21.9)
>20–40 years	83 (49.1)
>40 years	49 (29.0)
	Range 14.0–78.1; Mean 33.0
Sex	
Female	100 (59.2)
Male	69 (40.8)
Origin	
Caucasian	159 (94.1)
Other	8 (4.7)
Not stated	2 (1.2)
Follow-up, years	Range 1.00–10.43; Mean 4.15
Baseline severity	
Remission/mild	47 (27.8)
Moderate	46 (27.2)
Severe	69 (40.8)
Not stated	7 (4.1)
Baseline total IgE	
0–99 IU/ml	13 (7.7)
100–999 IU/ml	51 (30.2)
1,000–9,999 IU/ml	66 (39.1)
≥10,000 IU/ml	23 (13.6)
Not stated	16 (9.5); Range 3–98,100
	Mean 5,670; Median 1,501
Topical therapy	
TCS or TCS + tacrolimus	53 (31.4)
Tacrolimus monotherapy	116 (68.6)
Age of onset	
≤2 years	121 (71.6)
>2 years	34 (20.1)
Not stated	14 (8.3)
Asthma	
No	75 (44.4)
Yes	84 (49.7)
Not stated	10 (5.9)
Allergic rhinitis symptoms	
No	27 (16.0)
Yes	140 (82.8)
Not stated	2 (1.2)
Allergic conjunctivitis symptoms	
No	35 (20.7)
Yes	132 (78.1)
N/S	2 (1.2)
Skin-prick test positivities	
No	6 (3.6)
Yes, any	97 (57.4)
Yes, peanut	55 (32.5)
Not stated	66 (39.1)
History of HSV infections	
No	92 (54.4)
Yes	44 (26.0)
Not stated	33 (19.5)

Variable	*n* (%)
Hand eczema (any)	
No	38 (22.5)
Yes	120 (71.0)
Not stated	11 (6.5)
Palmar hand eczema	
No	68 (40.2)
Yes	38 (22.5)
Not stated	63 (37.3)
Food allergies	
No	43 (25.4)
Yes	121 (71.6)
N/S	5 (3.0)
Diagnosed contact allergies and the most common allergens	
No	97 (57.4)
Yes	31 (18.3)
Not stated	41 (24.3)
Nickel	11
Perfumes	11
Cobalt	5
Topical antimicrobials/antiseptics	5
Chrome	3
Lanolin	2
Preservatives	2
Current smoking	
No	124 (73.4)
Yes	4 (24.9)
Not stated	3 (1.8)
History of smoking	
No	96 (56.8)
Yes, <5 years	11 (6.5)
Yes, >5 years	45 (26.6)
Not stated	17 (10.1)
Regular use of inhalation corticosteroids	
No	137 (81.1)
Yes	31 (18.3)
Not stated	1 (0.6)
Regular use of oral antihistamine/montelukast	
No	153 (90.5)
Yes	15 (8.9)
Not stated	1 (0.6)
Oral antimicrobial medications due to AD	
No	39 (23.1)
Yes	124 (73.4)
Not stated	6 (3.6)
Current immunosuppressive medication (indication other than AD)	
No	162 (95.9)
Yes	6 (3.6)
Not stated	1 (0.6)
Adherence to treatment (endpoint evaluation)	
Poor	19 (11.2)
Average	53 (31.4)
Good	62 (36.7)
Not stated	35 (20.7)

AD: atopic dermatitis; IgE: immunoglobulin E; IU: International Units; TCS: topical corticosteroids; HSV: herpes simplex virus.

remission or a good treatment response were only 8.7% and 14.3%, compared with 51.6% and 79.7% in patients with IgE <1,000 IU/ml, and 36.9% and 58.1% in patients with IgE 1,000–10,000 IU/ml, respectively.

DISCUSSION

IgE is the scarcest of serum immunoglobulins, constituting only 0.0005% of the total free serum immunoglobulins in non-atopic adults, but the presence of elevated levels of serum total IgE is strongly associated with atopic disease (23, 24). Class switch to IgE in B cells is induced by allergen contact in conjunction with T-cell interaction and a T-helper type 2 cell polarized cytokine microenvironment (25). The half-life of free serum IgE is only 2–3 days and it has to be produced continuously in order to maintain its serum levels (26). Little is known about the source of IgE. It has been proposed that allergy

Table II. *Associations of variables with long-term outcome, adjusted analysis*

	Good treatment response		Complete remission	
Variable	Odds ratio	*p*-value	Odds ratio	*p*-value
Baseline total IgE				
0–999 IU/ml	1		1	
1,000–9,999 IU/ml	0.202	0.005	0.462	0.091
≥10,000 IU/ml	0.062	0.002	0.158	0.031
Contact allergies				
No	1		1	
Yes	0.162	0.007	0.287	0.048
Age, years	0.972	0.129	1.009	0.572
Asthma				
No	1		1	
Yes	0.779	0.641	0.516	0.754
Baseline clinical severity				
Remission/mild	1			
Moderate	3.929	0.069		
Severe	0.730	0.629		

effector organs (e.g. the lungs and the nasal mucosa) may be important sites of IgE production in allergic patients. IgE-producing cells have also been found in the blood, but their numbers are extremely low (27).

Previous studies have shown that total IgE levels are elevated in the majority of AD patients with moderate-to-severe disease, and a correlation between IgE levels and AD severity has been suggested in some studies (18, 19), but the results are partly conflicting (15, 28). Total IgE values at the age of 6–18 months seem to predict the subsequent visible AD at the age of 5 years in children (29).

In this study the most important factor predicting complete remission of AD and a good treatment response on the maintenance type of treatment, was serum total IgE. There was no correlation between baseline clinical severity of AD symptoms (IGA) and baseline total IgE in the patients studied. This may be because they were tertiary referral centre patients with a strong atopic diathesis who had already been treated by general practitioners and private dermatologists at baseline prior to follow-up in the specialized AD clinic. Also, due to the flaring nature of AD, a single-point evaluation of the clinical symptoms is often inadequate in defining the severity of the disease. In our data, the total IgE level predicted long-term treatment response much better than the baseline clinical picture. This finding is useful, as measurement of total IgE is easy and inexpensive and could be used to select patients who require closer follow-up in order to achieve a sufficient treatment response.

Median total IgE levels of the study patients decreased significantly during follow-up, showing an overall IgE response to the topical maintenance type of treatment. In patients with IgE values <10,000 IU/l at baseline, there was a trend towards a greater decrease in total IgE in patients who achieved complete remission, which is in concordance with previous studies showing a total IgE decrease in responders (30). Adherence to treatment appears to explain most of this trend, but it is a highly subjective variable in a non-blinded setting when assessed at the endpoint. No routine screening for parasite infections was done in these patients due to the very low total incidence (<10/100,000) of parasitic infections in Finland (31, 32). Hyper-IgE syndrome was clinically excluded in all patients with remarkably elevated IgE values.

In addition, contact sensitization appears to predict a poor outcome in long-term follow-up. At first glance this may seem surprising, since contact sensitization has been considered to be Th1 polarized in contrast to the Th2 polarization in AD, although recently it has been shown that atopic individuals may also have Th2 polarization in cases of contact sensitization (33). Also, it appears plausible that the larger the skin barrier defect, the greater the risk of contact sensitization (34). This group of patients may therefore represent a subgroup of AD patients with a more extensive skin barrier defect, which may explain the poor treatment response and long-term outcome. The mean total IgE values were slightly lower in patients with contact allergies, but regarding the prevalence of hand eczema or any other factor of the baseline clinical picture, these patients did not differ from patients with no contact sensitization. It is therefore unlikely that the more extensive patch-testing of patients with more severe symptoms would explain the association of contact allergies with poor outcome. Most (77%) of the patients with contact allergies were female, which is in concordance with previous studies concerning nickel as a common allergen (35); however, sex itself was not associated with outcome.

It is noteworthy that the proportion of patients with remission or, at most, mild AD symptoms, at the end of follow-up was 70%, indicating that good treatment results are possible, even in this kind of selected patient population with mostly moderate–severe AD and a high atopic diathesis, with topical maintenance type of therapy. None of the study patients were on systemic treatments at the end of follow-up and only a few had a history of systemic treatments. The effect of systemic medication in this study population can therefore be considered minor.

The retrospective setting and the selected tertiary referral centre study population were limitations of this study. The strengths of this study were the long follow-up time, the relatively large number of patients, and the real-life clinical setting.

These results have yet to be confirmed in a larger, prospective setting. Serum total IgE appears to be a promising biomarker in the treatment of AD, predicting long-term outcome. The association of delayed cell-mediated hypersensitivity with poor long-term outcome in AD may reflect greater, more treatment-resistant, and possible inflammation-independent defects in the skin barrier, increasing susceptibility to contact allergies.

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