

Are age-specific high serum IgE levels associated with worse symptomatology in children with atopic dermatitis?

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Abstract

Background Atopic dermatitis (AD) is a distressing disease associated with excoriations, pruritus, sleep disturbance, and elevation of serum total immunoglobulin E (IgE) levels.

Objective To evaluate whether serum IgE levels correlate with the symptomatology and plasma chemokine levels in children with AD.

Methods AD patients aged younger than 18 years were recruited from the pediatric dermatology clinic of a university teaching hospital, and the AD severity was evaluated using the SCORing Atopic Dermatitis (SCORAD) index. Concentrations of serum total IgE, eosinophil count, and plasma AD-associated chemokines [cutaneous T-cell-attracting cytokine (CTACK), thymus and activation-regulated chemokine (TARC)] were measured.

Results One hundred and seventeen Chinese children with AD (64 boys and 53 girls), with an age (mean $\pm$ standard deviation) of 10.7 ± 4.4 years, were recruited. Their overall SCORAD index (mean $\pm$ standard deviation) was 51.1 ± 22.8 . The total serum IgE level divided by the age-specific upper limit ($\bar{A}E$) correlated well with the extent and intensity of AD, except for oozing/crusting, which was significant only in males. There was a significant correlation between $\bar{A}E$ and pruritus or sleep loss only in females. Levels of IgE, CTACK, and TARC, and eosinophil count, differed significantly between patients with mild, moderate, and severe disease. $\bar{A}E$ correlated well with TARC ($r = 0.50$, $P < 0.001$) and eosinophil count ($r = 0.41$, $P < 0.001$), but not with CTACK ($r = 0.11$, $P = 0.270$). The prediction of moderate to severe eczema by $\bar{A}E$ gave an area under the receiver-operating characteristic curve of 0.76 (95% confidence interval, 0.65–0.86; $P = 0.004$). An optimum positive predictive value of 94.2% was achieved with a cut-off point of $\bar{A}E$ of 2.95, sensitivity of 75.0%, and specificity of 66.7%.

Conclusion $\bar{A}E$ correlates significantly with various objective clinical scores and chemokine markers of AD, and is a useful indicator for predicting moderate to severe AD in children.

Introduction

Atopic dermatitis (AD) is a distressing disease associated with pruritus and sleep disturbance. The overall severity of AD has been reported to correlate with the levels of serum immunoglobulin E (IgE);^{1,2} however, it is not known whether the subjective symptoms of pruritus and sleep loss or the objective signs of excoriations also correlate with the IgE levels. The symptomatology of AD is usually assessed using clinical scores. The SCORing Atopic Dermatitis (SCORAD) index is a clinical score widely used in Europe for the assessment of AD severity. It measures the extent, intensity, pruritus, and sleep loss related to AD over the preceding 3 days.^{3,4} The severity of AD has also been found to be associated with the levels of various chemokines.^{5–7} These chemokine markers

have been extensively studied in both adults and children. Specifically, the levels of AD-associated chemokines [cutaneous T-cell-attracting cytokine (CTACK), thymus and activation-regulated chemokine (TARC)] are correlated with various clinical signs and severity of eczema in children.^{5–8} This study evaluated whether serum IgE levels were associated with: (i) the components of the SCORAD index; and (ii) the levels of CTACK and TARC.

Patients and Methods

The results of all patients whose eczema severity had been measured using the SCORAD index and serum IgE and plasma chemokine levels, between August 2003 and June 2005, were analyzed. AD patients aged younger than 18 years managed in the

Table 1 Immunoglobulin E (IgE), $\bar{A}E$, and SCORing Atopic Dermatitis (SCORAD) index by gender

	Females (n = 53)	Males (n = 64)	All patients (n = 117)
Age (years), mean (SD)	10.4 (3.5)	11.02 (5.0)	10.7 (4.4)
Total SCORAD, mean (SD)	49.2 (22.1)	52.72 (23.5)	51.1 (22.8)
Objective SCORAD, mean (SD)	36.80 (19.3)	40.7 (21.3)	38.9 (20.4)
Serum log-transformed IgE concentration, mean (SD)	3.2 (0.8)	3.3 (0.7)	3.2 (0.8)
$\bar{A}E$	32.5 (50.0)	35.7 (72.5)	34.2 (63.1)

SD, standard deviation. Three males and five females had normal serum total IgE (i.e. $\bar{A}E < 1$).

Table 2 Correlations (r) between $\bar{A}E$ and SCORing Atopic Dermatitis (SCORAD) components by gender

	r		
	Females (n = 53)	Males (n = 64)	All patients (n = 117)
Objective SCORAD	0.523†	0.468†	0.482†
Extent	0.565†	0.436†	0.476†
Intensity	0.482†	0.463†	0.465†
Erythema	0.496†	0.365†	0.406†
Edema/papulation	0.421†	0.437†	0.424†
Oozing/crusting	0.112	0.309*	0.236*
Excoriations	0.463†	0.432†	0.436†
Lichenification	0.306*	0.352†	0.332†
Dryness	0.367†	0.369†	0.361†
Pruritus	0.321*	0.101	0.183*
Sleep loss	0.336*	0.127	0.197*

* $P < 0.05$.

† $P < 0.01$.

pediatric dermatology clinic of a university teaching hospital were recruited. AD was diagnosed according to criteria proposed by Hanifin and Rajka,⁹ and the AD severity was evaluated clinically using the SCORAD index.^{3,10} Patients were excluded if information regarding pruritus or sleep loss could not be recalled by the caregivers. Informed consent was obtained from parents, and the Clinical Research Ethics Committee of the university approved the study.

Peripheral blood (PB) was collected from the recruited AD patients, centrifuged at 4 °C and 2000 *g* for 10 min, and then stored at –80 °C until analysis in one batch. Plasma concentrations of AD-associated chemokines (CTACK and TARC)⁷ were measured by enzyme-linked immunosorbent assay (R & D Systems, Minneapolis, MN, USA). The lowest detection limits for these inflammatory markers were 1.6 and 7.0 pg/mL, respectively. The serum concentration of total IgE was measured by microparticle immunoassay (IMx analyzer, Abbott Laboratories, Abbott Park, IL, USA), and expressed as $\bar{A}E$, which was defined as the total serum IgE level divided by the age-specific upper limit of a local reference. Eosinophil counts in PB were evaluated using a Coulter STKS counter (Beckman-Coulter, Miami, FL, USA). TARC, CTACK, and $\bar{A}E$ were log-transformed and eosinophil counts were square-rooted to achieve normality before analysis. The correlations between IgE and different SCORAD components were calculated

using Pearson's and Spearman's correlations as indicated, whereas the Kruskal–Wallis H-type test was used to compare serum IgE, plasma chemokines, and eosinophil levels between the three severity groups. All statistical tests were performed with SPSS 13.0. Comparisons were two-tailed, and P values of less than 0.05 were considered to be statistically significant. A receiver-operating characteristic (ROC) curve was generated to evaluate how well IgE levels could predict subsequent eczema severity.

Results

One hundred and seventeen ethnic Chinese AD patients (64 boys and 53 girls) with an age (mean $\pm$ standard deviation) of 10.7 ± 4.4 years were recruited (Table 1). None of the patients received any systemic corticosteroid or immunomodulatory treatment before being enrolled in the study. They were treated with emollients and topical corticosteroids as needed. The overall SCORAD index (mean $\pm$ standard deviation) for the AD patients was 51.1 ± 22.8 , and eczematous skin affected 2.5–98.5% of the body surface area.

Serum log-transformed IgE levels correlated with the objective SCORAD index¹⁰ (Fig. 1). Table 2 illustrates the correlations between $\bar{A}E$ and different SCORAD components for all

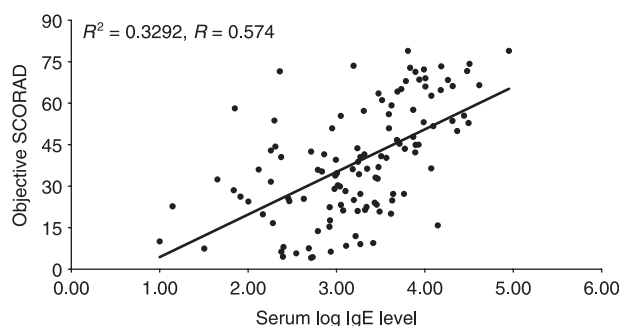


Figure 1 Scatter plot showing the correlation between the objective SCORing Atopic Dermatitis (SCORAD) index and serum log-transformed immunoglobulin E (log IgE) levels ($n = 117$)

patients by gender. The objective signs (extent and intensity) correlated better than the subjective symptoms (pruritus and sleep loss) reported by parents with the log-transformed $\bar{A}E$ value (objective: $r = 0.476$ and $r = 0.465$, respectively; $P < 0.01$; subjective: $r = 0.183$ and $r = 0.197$, respectively; $P < 0.05$). Except for several intensity components, better correlations between the various parameters were observed in females than in males. The log-transformed $\bar{A}E$ value showed a significant correlation with pruritus and sleep loss for females ($r = 0.321$ and $r = 0.336$, respectively; $P < 0.05$), but not for males ($r = 0.101$ and $r = 0.127$, respectively).

Eighty-two (70%) patients reported a history of allergic rhinitis, and 35 (30%) patients reported a history of asthma or hyperactive airway disease. In the subgroup of patients who had never experienced allergic rhinitis, asthma, or urticaria ($n = 26$), the log-transformed $\bar{A}E$ value correlated well with the objective SCORAD index (Spearman's $\rho = 0.554$, $P = 0.003$).

The plasma CTACK and TARC levels of the 117 patients were also measured. The plasma CTACK and TARC concentrations (mean $\pm$ standard error, pg/mL) were 753 ± 61 and 886 ± 125 , respectively. The eosinophil percentage present in

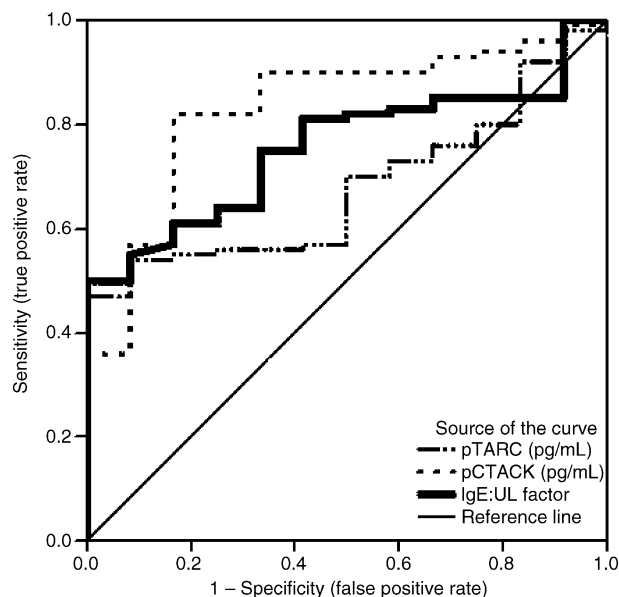


Figure 2 Receiver-operating characteristic (ROC) curves of eczema severity prediction by $\bar{A}E$ values, and thymus and activation-regulated chemokine (TARC) and cutaneous T-cell-attracting cytokine (CTACK) levels. Areas under the ROC curves for $\bar{A}E$, TARC, and CTACK are 0.756 [95% confidence interval (CI), 0.65–0.86; $P = 0.004$], 0.678 (95% CI, 0.56–0.99; $P = 0.044$), and 0.833 (95% CI, 0.72–0.94; $P < 0.001$), respectively

blood (mean $\pm$ standard error) was $9.3 \pm 0.5\%$. The eosinophil count (mean $\pm$ standard error) was $(0.80 \pm 0.10) \times 10^9/L$. The levels of these markers were significantly different between the three severity grades (Table 3). The log-transformed $\bar{A}E$ value correlated well with the log-transformed TARC level ($r = 0.50$, $P < 0.001$) and the square-root eosinophil count ($r = 0.41$, $P < 0.001$), but not with the log-transformed CTACK level ($r = 0.11$, $P = 0.270$).

A ROC curve was generated to see how well $\bar{A}E$ could predict eczema severity (Fig. 2). From the ROC curve, the $\bar{A}E$

Table 3 Levels of $\bar{A}E$, eosinophils, and chemokines [cutaneous T-cell-attracting cytokine (CTACK) and thymus and activation-regulated chemokine (TARC)] for patients with mild, moderate, and severe atopic dermatitis. All results are expressed as mean (standard error)

	Objective SCORAD			Kruskal–Wallis P
	Mild (< 15) ($n = 15$)	Moderate (15–40) ($n = 47$)	Severe (> 40) ($n = 55$)	
$\bar{A}E$	5.32 (1.27)	12.58 (2.36)	60.59 (11.26)	< 0.001
Plasma CTACK (pg/mL)	284 (60)	692 (92)	912 (93)	< 0.001
Plasma TARC (pg/mL)	244 (42)	448 (120)	1419 (221)	< 0.001
Eosinophil (%)	6.6 (1.0)	8.1 (0.7)	11.1 (0.8)	0.002
Eosinophil count ($\times 10^9/L$)	0.48 (0.08)	0.64 (0.06)	1.04 (0.20)	0.002

SCORAD, SCORing Atopic Dermatitis.

prediction of moderate to severe eczema (recognized as an objective SCORAD index of 15) was significant, achieving an area under the curve of 0.76 [95% confidence interval (CI), 0.65–0.86; $P = 0.004$]. An optimum positive predictive value of 94.2% was achieved with a cut-off point of $\bar{A}E$ of 2.95. This cut-off point had a sensitivity of 75.0% and specificity of 66.7%. ROC curves for the chemokines were also plotted, with areas under the curves for TARC and CTACK of 0.68 (95% CI, 0.56–0.89; $P = 0.044$) and 0.83 (95% CI, 0.72–0.94; $P < 0.001$), respectively.

Discussion

Serum IgE levels correlate significantly with the extent and intensity of AD. They also correlate well with the various objective components of the SCORAD index, but poorly with the symptoms of pruritus or sleep loss and the sign of oozing/crusting. Furthermore, IgE levels show good correlations with TARC, which is a chemokine marker of disease severity. These findings are consistent with our previous observations that the subjective symptoms of sleep loss and pruritus are generally poorly correlated with various objective clinical and chemokine markers.⁴

Our finding that the severity of AD correlates with serum IgE levels is in agreement with that of Laske *et al.*;¹ however, we used $\bar{A}E$ and recorded better correlations. The use of crude IgE values without the consideration of age-specific references may be misleading and may undermine the usefulness of this readily available parameter for atopy. An age-dependent increase in serum IgE has been reported in various populations, and boys show higher total IgE values at each age;^{11–13} however, this sex difference is not statistically significant within the group of atopic children.¹¹ Our study also confirms that there is no significant sex difference in IgE levels in children with AD. Using $\bar{A}E$, we did not find any correlations with age. The present cohort consisted of AD children with increased IgE, with only eight of the whole study population having a normal IgE level for age ($\bar{A}E < 1$). It would be interesting to evaluate whether a similar observation between AD severity and serum IgE could be found in adults, or those with intrinsic type AD (with normal IgE).

It is not certain whether serum IgE is useful in predicting disease severity in other atopic disorders, such as asthma and rhinitis. Hetman *et al.*¹³ reported a correlation between IgE levels and the number of positive skin tests, peripheral eosinophilia, asthma, and other atopic diseases. $\bar{A}E$ may also be determined in these atopic conditions to assess its usefulness as a marker of disease severity. In the subgroup of AD patients without allergic rhinitis or asthma, we also found good correlations between $\bar{A}E$ and the objective SCORAD index.

In this study, we did not explore infective factors and IgE levels. Nasal *Staphylococcus aureus* colonization has been reported to be associated with high eosinophil counts and IgE

levels,¹⁴ and specific IgE antibodies to staphylococcal enterotoxins have been identified in the serum of patients with AD.¹⁵ Colonization with superantigen-producing *S. aureus* was associated with increased severity of AD, but superantigen production by *S. aureus* was inversely correlated with total IgE concentration.¹⁶ We have recently reported that the SCORAD index and eosinophil count, but not IgE levels, are all significantly higher in children with significant ($\geq 10^4$ colony-forming units per milliliter) nasal carriage of *S. aureus*.¹⁷ Therefore, $\bar{A}E$ may reflect disease severity independent of *S. aureus* carriage or colonization.

The present study shows that $\bar{A}E$ correlates well with the objective clinical and serum TARC level, and may serve as an overall marker for disease severity. Furthermore, $\bar{A}E = 2.95$ predicts moderate to severe disease. Indeed, the ROC curve for $\bar{A}E$ lies in between that for the two chemokines TARC and CTACK. Unlike the chemokines, serum IgE measurement is inexpensive and readily available in most clinical services. In conclusion, IgE is both a laboratory marker for atopy and a parameter of disease severity. Further investigation and confirmation of its significance in adult AD patients and in diseases showing atopic phenotypes are warranted.

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