

IgE in Atopic Dermatitis: A Study of the Intercellular Fluid

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In 33 adult patients with atopic dermatitis of mild to severe degree the concentration of IgE in serum (S) and intercellular fluid (IF) was studied by suction blister technique. The median value of IF/S-IgE was 0.20 and not different from the ratio 0.21 found in controls. Furthermore, by subdividing the patients into groups with asthma/rhinitis or different severities of eczema no significant differences in the IF/S-IgE ratios were found compared with the controls. In the controls the IF/S-IgE ratio (0.21) was significantly different from the IF/S-IgG ratio (0.32). The median ratio of IF/S-IgE divided by IF/S-IgG was 0.63, which might indicate a reduced passage of IgE into IF compared with IgG presumably dependent on differences in the molecular size or tertiary structure of the proteins. *Key word: Suction blister.* (Received February 19, 1987.)

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In atopic dermatitis (AD), the level of serum IgE (S-IgE) is often increased, especially in individuals with concomitant respiratory allergy. The highest values are found in atopic patients with AD (1). The elevation of S-IgE seems roughly to parallel the extent and severity of the dermatitis (2-3). However, about 20% of patients with severe flexural eczema have a normal S-IgE concentration (4). Thus, the role of IgE mast-cell-mediated allergy in AD remains open for discussion, and the possible role of IgE in the pathogenesis is unknown. As the skin is the target for the possible pathogenic action of IgE in AD, analyses of the level of IgE in suction blister fluid from normal and atopic skin was measured by the blister technique described by Kiistala (5).

MATERIAL AND METHODS

Patients

Thirty-three adult patients (12 males, 21 females) with atopic dermatitis of various degrees were investigated. Six patients had a severe wide-spread dermatitis, 16 had a moderate and 11 patients a mild dermatitis with mainly flexural eczema. The mean age was 27.3 years (range 15-73). Eleven patients had concomitantly asthma and/or rhinitis. As a control group 9 non-atopic volunteers (6 males and 3 females), mean age 27 years (range 22-34), without skin diseases were studied. All patients in the eczema group were treated with topical steroids and/or coal tar at the time of investigation. However, treatment of the test site on the abdominal skin was avoided.

Suction blister method

One or two perspex cups with diaphragms perforated by 18 holes (5 mm diameter) were placed on the lower abdominal skin. A steady negative pressure of 300-400 mmHg was established by a pump. In normal skin, usually within 2 h, small vesicles appeared, coalescing to form bullae filling the entire holes (5). In AD, skin blisters often ruptured very early and the fluid dispersed in the cup. This occurred in spite of the fact that only non-eczematous skin was exposed to suction. In cases with fully developed blisters the exudate was removed using a syringe with a polystyrene point. The blister fluid and serum samples were stored at -18°C until measurements of IgE and IgG were performed. In some cases the blister fluid was examined for the content of albumin and the presence of cells (6).

Analytical methods

The IgE concentrations (MW 190000) (KU/l) in the intercellular fluid (IF-IgE) and serum (S-IgE) were determined in all persons using a commercially available radioimmunoassay (IgE, RIA 100, Pharmacia). IgG (MW 160000) (g/l), in IF and serum was determined routinely on Cobas Fara (Roche).

Statistical methods

Each sample was run in duplicate. The analytical coefficient of variation (CV%) was dependent on the S-IgE concentration according to the following intervals (S-IgE: 0–50 KU/l, CV%: 0.11–0.17; S-IgE: 51–500 KU/l, CV%: 0.038–0.084; S-IgE >500 KU/l, CV%: 0.077). For S-IgG the CV% was 0.03. Statistical methods were computation of Spearman's coefficient of rank correlation and Wilcoxon's test.

RESULTS

In the control group the following median values were found: S-IgE=26 KU/l and IF-IgE=4 KU/l. In the AD group S-IgE was 360 KU/l, IF-IgE 140 KU/l. The concentrations found when subdividing the patients according to severity of eczema with or without asthma/rhinitis are given in Table I together with the ratio of IF/S-IgE. Twenty-seven per cent of the AD patients without asthma and/or rhinitis had S-IgE <130 KU/l.

Compared with the controls the ratio of IF/S-IgE was not different neither in the AD group (Wilcoxon's test, $p>0.05$) nor in the subgroup with respiratory allergy ($p>0.05$).

Table I. *IgE in serum (S) and intercellular fluid (IF) of clinically uninvolved skin in atopic dermatitis (AD) and controls*

Values are expressed as medians with ranges in parenthesis. BA=bronchial asthma, AR=allergic rhinitis, -/+ means absence or presence of respective disease

	S-IgE (KU/l)	IF-IgE (KU/l)	IF/S-IgE
Control group <i>n</i> =9	26 (2–126)	4 (2–28)	0.21 (0.02–1.0)
AD group <i>n</i> =33	360 (15–16 800)	140 (2–2 880)	0.20 (0.07–0.91)
AD + BA/AR <i>n</i> =11	390 (257–16 800)	140 (15–2 880)	0.23 (0.07–0.39)
AD – BA/AR <i>n</i> =22	250 (15–13 600)	85 (2–2 200)	0.20 (0.13–0.91)
AD Mild <i>n</i> =11	130 (15–797)	21 (2–142)	0.18 (0.07–0.61)
AD Moderate <i>n</i> =16	660 (45–13 600)	170 (30–2 200)	0.21 (0.10–0.91)
AD Severe <i>n</i> =6	3 900 (325–16 800)	980 (102–2 880)	0.29 (0.17–0.35)

Table II. *IgG in serum (S) and intercellular fluid (IF) in the skin of 9 normal controls*

Values are expressed as medians with ranges in parenthesis

S-IgG (g/l)	IF-IgG (g/l)	IF/S-IgG	IF/S-IgE IF/S-IgG
9.3 (6.5–10.9)	3.0 (1.5–5.5)	0.32 (0.2–0.55)	0.63 (0.06–2.93)

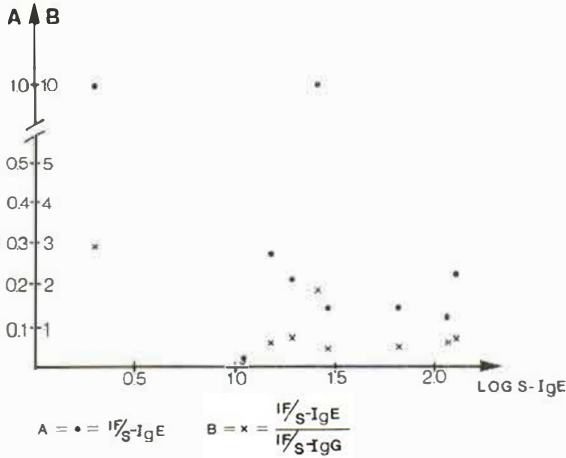


Fig. 1. The ratio of IF/S-IgE and IF/S-IgE/IF/S-IgG plotted as a function of S-IgE in the control group ($n=9$).

Similarly non-significant differences were observed when comparing subgroups according to severity of eczema ($p>0.05$).

The S-IgG concentrations in the control group (Table II) were approximately three times the IF-IgG values giving a median ratio of 0.32. The double ratio of IF/S for IgG and IgE had a median value of 0.63 characterized by a wide variation from 0.06–2.93. However, as shown in Fig. 1 only two values exceeded 1. On the other hand the coefficients of correlation between IF and S for IgE and IgG were $r=0.65$ and 0.68 respectively, which indicates the existence of a relationship between the concentration in serum and intercellular fluid for both molecules.

The ratio of IF/S-IgE plotted as a function of S-IgE (Figs. 1 and 2) showed a tendency to high values with low S-IgE concentrations for some of the AD patients as well as the controls.

The concentration of albumin in the IF determined regularly in the course of the investigation varied between 9–16 g/l. Microscopical examination showed only a few cells in the blister fluid.

DISCUSSION

Previous determinations of IgE in the skin (7) showed mean values of 16 U/ml in saline extracts of normal skin biopsies, 14 U/ml in uninvolved psoriatic skin, 34 U/ml in

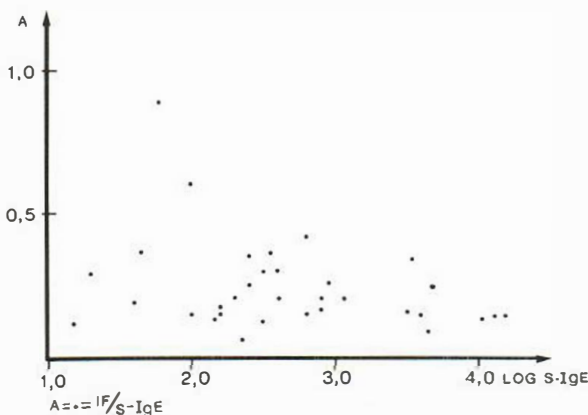


Fig. 2. The ratio of IF/S-IgE in the eczema patients plotted individually as a function of S-IgE ($n=33$).

uninvolved AD skin and 44 U/ml in lesional AD skin (7). As other techniques were used in our investigations, the values obtained cannot be compared directly. However, the same tendency to much higher serum levels of IgE in comparison with the levels in blister fluid and saline extracts, were found.

In our investigation S-IgE and IF-IgE in atopic skin varied from normal values to concentrations several times that observed in normal skin. However, the ratios of IF/S-IgE in the AD group did not differ from the control ratios.

In theory, the suction blister technique produces a filtration of plasma from the vessels into the skin. A mere leakage from the vessels or presentation of an IgE fraction produced or bound cellularly can be excluded due to the fact that low albumin concentrations and only a few cells were found in the blister fluid (8-10). Therefore, the elevated IF-IgE may result from a free fraction of IgE passing from the vessels into the intercellular fluid. An increased leakage into IF from the dermis, through dilated lymph vessels in inflamed skin is unlikely as the ratios were similar in the different eczema subgroups. The question to be answered is therefore, what mechanisms are involved in regulation of IgE passage through the vessel wall?

As seen from Fig. 1 the distribution of the ratio of IF/S-IgE in the control group gives the impression of an exponential curve with high IF/S-IgE ratios at low S-IgE values. In the AD group (Fig. 2) with high values of S-IgE a tendency towards exponentiality was noticed as well. At higher S-IgE values a constant ratio of IF/S-IgE=0.15-0.20 was found suggesting a steady state filtration of IgE across the capillary wall. In this context, raised ratios at low S-IgE values might be indicative of an active transport mechanism.

In order to elucidate this further we have measured IgG in serum and IF in the control group. This immunoglobulin has nearly the same molecular weight as IgE. The results showed the median ratio of IF/S-IgG to be 0.32 (Table II) which is significantly higher than the ratio of IF/S-IgE=0.21 ($r=0.64$, Spearman's coefficient, $p<0.05$). Furthermore, the median ratio of IF/S-IgE divided by IF/S-IgG was 0.63 (Fig. 1, Table II) and showed a wide variation. This may be attributed to the considerable individual variation in IF/S-IgE (0.02-1.0) and not from IF/S-IgG which showed a more narrow range (0.20-0.55). The suction blister technique as such does not seem to cause the variation, since it was found for the IgE protein only.

The underlying mechanisms, that elicit the observed differences, deserve further investigation. The possibility exists that peripheral lymph composition is highly variable under various conditions in the skin. In any case, our median ratio of 0.63 points to an enhanced passage of IgG into IF compared to IgE since the IgE/IgG ratio was expected to be 1 if both molecules were transported proportionally across the capillary wall. This enhanced passage may be related to differences in molecular weight, molecular size, or in the tertiary structure of the proteins. However, involvement of another transport mechanism for IgE than simple filtration, especially at low S-IgE values, cannot be excluded.

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