

ANTI-IgE AUTOANTIBODY IN PATIENTS WITH ATOPIC DERMATITIS¹

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The anti-IgE autoantibody in the IgG class was detected in 39/45 (86.7%) patients with atopic dermatitis by using a newly established solid-phase enzyme immunoassay. The ϵ -chain specificity of the anti-IgE autoantibody was confirmed by competitive inhibition by using human IgG, IgA, IgM, IgD, IgE, and heat-denatured IgE protein. Significant correlations were observed between the levels of the anti-IgE autoantibody and the serum IgE. Gel filtration studies indicated that the anti-IgE autoantibody in sera from atopic dermatitis was mainly present in the form of an immune complex with self IgE. The role of the IgE-anti-IgE immune complex and the role of the anti-IgE autoantibody in the modulation of the IgE-mediated immune system in atopic dermatitis are discussed.

Atopic dermatitis, along with atopic bronchial asthma, is a representative atopic disorder. The precise mechanisms involved in the development of these diseases, particularly atopic dermatitis, are unknown. We have reported that significant amounts of anti-IgE autoantibody of the IgG class and the immune complex with self IgE were present in sera from patients with bronchial asthma, and we found that this autoantibody induced a reversed-type immediate skin reaction (1). We now report evidence for the presence of the anti-IgE autoantibody and the IgE-anti-IgE immune complex in sera from patients with atopic dermatitis, and the role of this antibody in atopic dermatitis is discussed.

MATERIALS AND METHODS

Patients and sera. Forty-five patients with atopic dermatitis were studied. Twelve of those had bronchial asthma, and 33 did not. Seventeen disease-free individuals with no symptoms or history of allergy, and with low serum total IgE levels (less than 100 IU/ml) served as the controls. Atopic dermatitis patients were monitored at the Department of Dermatology, Kansai Medical University. All sera were stored at -20°C until use, and were centrifuged at 30,000 × G for 30 min at 4°C just before application.

Preparation of IgE. IgE myeloma protein, which was used as the antigen for the enzyme immunoassay (EIA),³ was isolated from the

sera of two patients with IgE myeloma [IgE(NS) (2), and IgE(KZ)]. After salt fractionation with 50% saturated ammonium sulfate, IgE protein was isolated by diethylaminoethyl (DEAE)-cellulose (Whatman Inc., Clifton, NJ) column chromatography, followed by gel filtration with Sephadex G-200 (Pharmacia Fine Chemicals, Uppsala, Sweden) (3). The purity of isolated IgE was confirmed by EIA with the use of monospecific antibodies. Ig other than IgE were not present in this preparation. IgA and IgD myeloma proteins were also isolated by using the same procedures. IgM was obtained from Cappel Laboratories, Inc. (Cochranville, PA). IgG was purified from normal human pooled sera by salt fractionation with 33% saturated ammonium sulfate, followed by DEAE-cellulose column chromatography.

Enzyme immunoassay (EIA). Antibody against IgE was measured by a solid-phase EIA, as described (1). Each well of polyvinylchloride microtiter plates (Dynatech Laboratories, Alexandria, VA) was first coated with 50 μ l of purified IgE, (20 μ g/ml in 0.01 M phosphate-buffered saline (PBS), pH 7.4) by incubation overnight at 4°C. After three washes in PBS, 200 μ l of 10% fetal calf serum (FCS) solution were added to each well, and the preparations were then incubated for 1 hr at room temperature to block nonspecific binding of Ig to the well surfaces. After five washes in PBS, 50 μ l of serum to be tested (diluted 1/10 to 1/50 with PBS containing 0.05% Tween 20 (PBS-Tween) and 10% FCS) were added to each well in triplicate, and the preparations were incubated overnight at 22°C. After 10 washes in PBS-Tween, 50 μ l of alkaline phosphatase (Sigma Chemical Co., St. Louis, MO)-labeled mouse monoclonal anti-human IgG (Wako Chemical Co., Tokyo, Japan) were added to each well, and the plates were incubated for 1 hr, after which 100 μ l of para-nitrophenyl phosphate (Sigma) in 1 M diethanolamine buffer, pH 9.0, were added to each well. After a 1-hr incubation, the OD was measured at 405 nm by using a Microelisa Auto Reader, MR 580 (Dynatech). The IgE binding activity of each serum was presented as OD counts after subtracting the background (the count in wells without IgE myeloma protein as an antigen). The activity of anti-IgE antibody of the IgG class was expressed as a unit of the standard serum containing 100 U/ml of antibody that corresponded to approximately 100 ng/ml of IgG, as measured by a solid-phase EIA.

Inhibition study. The specificity of anti-IgE antibody was determined by a competitive inhibition EIA. A mixture of 100 μ l of each of the inhibitors (IgG, IgA, IgM, IgD, IgE, and heat-denatured IgE) at varying dilutions, and the samples to be tested, were incubated overnight at 22°C. Before inhibition, the test samples were diluted to 50% of the maximum IgE binding. The results of the inhibition were expressed as the percent inhibition of IgE binding activity, calculated as follows:

% inhibition

$$= \left(1 - \frac{\text{OD 405 nm count in the presence of inhibitor} - \text{background}}{\text{OD 405 nm count in the absence of inhibitor} - \text{background}} \right) \times 100$$

The background represents the count in wells without IgE myeloma protein as an antigen.

Heat-denatured IgE was prepared by heating IgE(KZ) myeloma protein at 56°C for 4 hr. After centrifugation at 30,000 × G for 30 min, this preparation was used for the inhibition study.

Gel filtration. Six milliliters of each diluted serum were chromatographed at 4°C on a 2.6 × 100 cm Sephacryl S-300 (Pharmacia) column developed with 0.01 M PBS, pH 7.4, at 10.7 ml/hr, and 3 ml fractions were collected. Eluates were monitored by OD measurement at 280 nm. The value of anti-IgE autoantibody and the total IgE level were examined in each fraction.

Serum IgE. Total serum IgE levels were determined by using paper radioimmunosorbent test (Pharmacia).

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³ Abbreviation used in this paper: EIA, enzyme immunoassay.

Statistical analysis. Statistical analysis was performed by using Student's *t*-test.

RESULTS

Anti-IgE antibody in atopic dermatitis. We examined sera from the 45 atopic dermatitis patients with or without bronchial asthma, and the sera from the 17 normal individuals for their ability to bind to IgE proteins. The values of anti-IgE autoantibody for each group are presented in Figure 1. The sera from 39 of 45 (86.7%) patients with atopic dermatitis showed positive IgE binding. The magnitude of the anti-IgE autoantibody was significantly different between normal controls (2.07 ± 1.48 U) and patients with atopic dermatitis (56.8 ± 54.2 U, $p < 0.001$). There was no significant difference between the findings in those patients with atopic dermatitis plus bronchial asthma (68.6 ± 56.0 U) and those with atopic dermatitis alone (52.4 ± 52.8 U) (Figure 1).

Specificity of anti-IgE antibody. Competitive inhibition studies were done to confirm the specificity of this anti-IgE autoantibody with the use of human Ig of each isotype (IgG, IgA, IgM, IgD, and IgE) as inhibitors. Representative inhibition curves from the serum of a patient with atopic dermatitis are illustrated in Figure 2. The IgE binding of this serum was inhibited by two IgE myeloma proteins of different origins (IgE(NS) and IgE(KZ)). In contrast, the other Ig (IgG, IgA, IgM, and IgD) showed no inhibitory effects on the IgE binding of this serum.

To additionally clarify the IgE binding property of this antibody, we used heat-denatured IgE as an inhibitor for

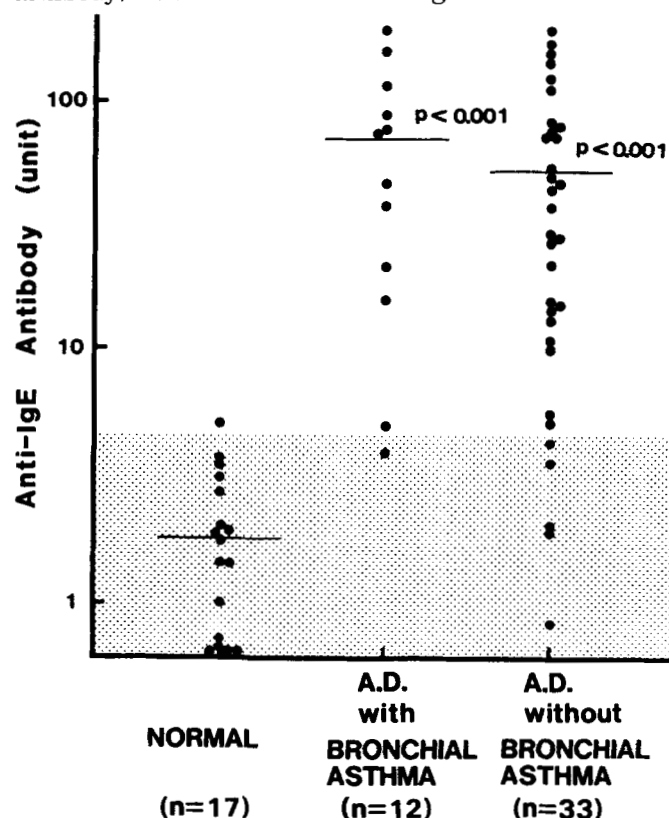


Figure 1. The levels of anti-IgE autoantibody in sera from 45 patients with atopic dermatitis (A.D.) (12 cases with bronchial asthma and 33 cases without it) and 17 healthy individuals, as detected by a solid-phase EIA. The values of anti-IgE autoantibody of the IgG class are expressed as a unit of the standard serum containing 100 U/ml of antibody that corresponded to 100 ng/ml of IgG. The shaded area represents the mean $\pm$ 2 SD for the control group. The horizontal bars indicate the means.

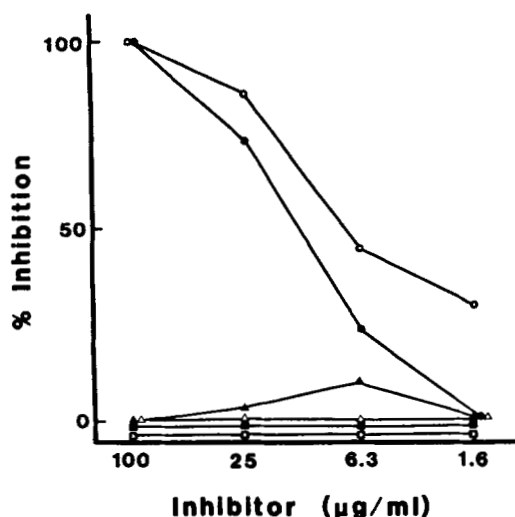


Figure 2. Representative competitive inhibition EIA with one atopic dermatitis serum. A mixture of 100 μ l each of the inhibitors (IgG (Δ), IgA ($\blacktriangle$), IgM ($\square$), IgD ($\blacksquare$), IgE(NS) ($\circ$), and IgE(KZ) ($\bullet$)) at indicated dilutions and serum to be tested were incubated overnight at 22°C and were applied to a solid-phase EIA as described in *Materials and Methods*. Before inhibition, the test sample was diluted to 50% of the maximum IgE binding. The results of inhibition are expressed as the percent inhibition of serum IgE binding activity in the absence of inhibitor.

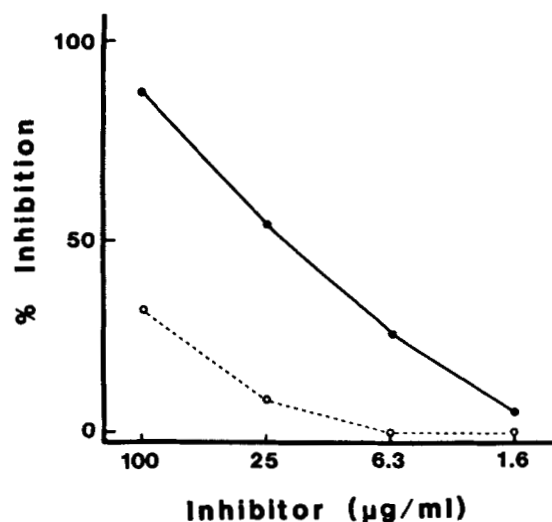


Figure 3. Competitive inhibition EIA with the use of heat-denatured ($\circ$) and intact ($\bullet$) IgE as inhibitors. IgE protein was denatured by heating at 56°C for 4 hr, and then centrifuging at $30,000 \times G$ for 30 min. The same competitive inhibition EIA that was described in Figure 2 was performed.

the same inhibition study. As shown in Figure 3, the IgE binding activity of this serum was completely inhibited by intact IgE myeloma protein (IgE(KZ)) but not by heat-denatured IgE protein. When heated to 56°C for 4 hr, IgE protein is known to lose the antigenicity of the Fc portion (De2) (4). These results support the proposed concept of the IgE (Fc) binding specificity of the anti-IgE autoantibody in patients with atopic dermatitis.

Relation of anti-IgE autoantibody to serum IgE levels. The relationship of the values of anti-IgE autoantibody to the total IgE levels of these sera was examined. As illustrated in Figure 4, significant correlations were noted between the values of anti-IgE autoantibody and the serum total IgE levels among all sera from patients with atopic dermatitis ($n = 45$, $r = 0.634$, $p < 0.001$), among those without bronchial asthma ($n = 33$, $r = 0.648$, $p < 0.001$), and among those with bronchial asthma ($n = 12$,

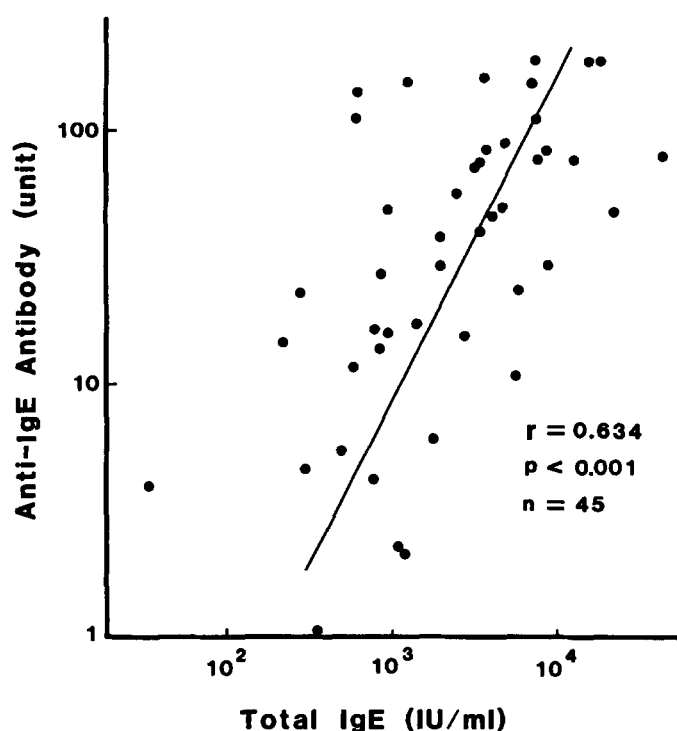


Figure 4. The correlation between total IgE levels and the anti-IgE autoantibody as measured by the paper radioimmunosorbent test and solid-phase EIA, respectively.

$r = 0.651$, $p < 0.05$). There was no significant correlation among the normal controls ($n = 17$, $r = -0.40$).

IgE-anti-IgE immune complex. Gel filtration analyses by Sephacryl S-300 were carried out with the use of sera which revealed high values of the anti-IgE autoantibody, and the total IgE antibody from patients with atopic dermatitis. The anti-IgE autoantibody of the IgG class was detected as a single peak at the position of a large molecule of about 600,000 daltons, and was not detected at the position of monomeric IgG (Figure 5C). The IgE protein was observed as two peaks, one major peak of monomeric IgE and another minor peak of a complexed form that corresponded with the peak of anti-IgE autoantibody, thereby suggesting the presence of an IgE-anti-IgE immune complex (Figure 5B). After heating at 56°C for 4 hr, the same sample was applied to the column. The anti-IgE autoantibody was detected only at the position of monomeric IgG instead of the position of the large molecule that was found in Figure 5C (Figure 5D). These results strongly suggest that the anti-IgE autoantibody in sera from patients with atopic dermatitis is present mainly in the immune complex form with self IgE.

DISCUSSION

We have found evidence of an autoantibody that reacts exclusively with human IgE present in the sera of patients with bronchial asthma, especially in those with atopic asthma (1). In this study, we also detected significant amounts of anti-IgE autoantibody in sera from patients with atopic dermatitis in the absence or presence of bronchial asthma, and the magnitude of the anti-IgE autoantibody in atopic dermatitis was almost as extensive as in atopic asthma. The ϵ -chain specificity of the anti-IgE autoantibody was confirmed in the competitive

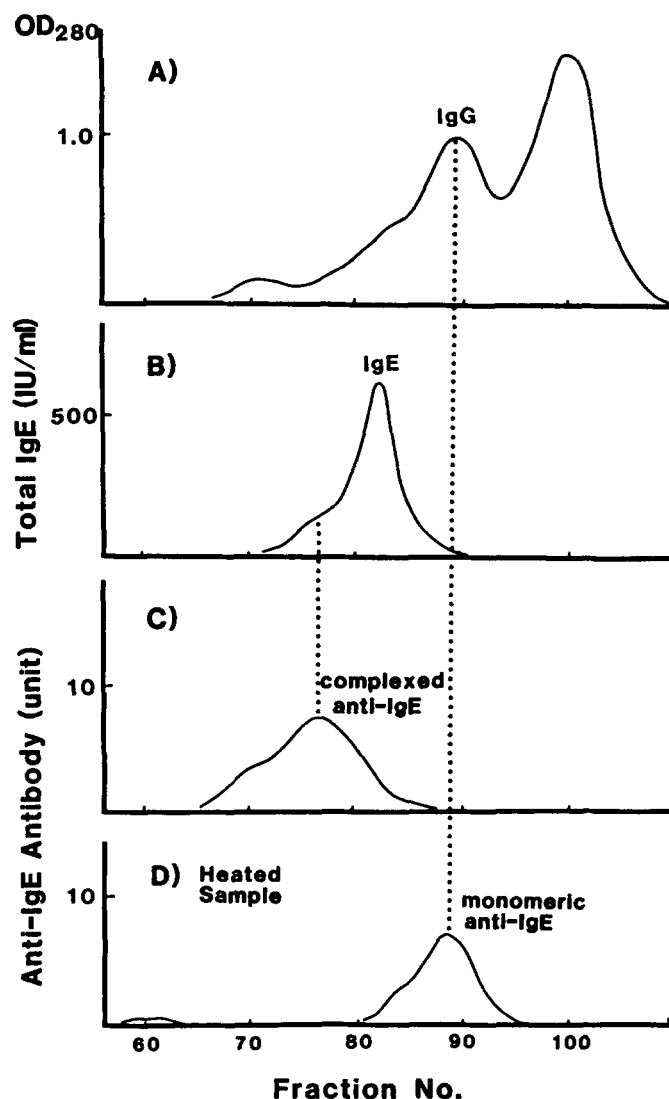


Figure 5. A representative gel filtration analysis by Sephacryl S-300 with the use of serum from a patient with atopic dermatitis with high IgE and anti-IgE autoantibody levels. Six milliliters of the diluted serum were applied at 4°C on a 2.6 x 100 cm column developed with 0.01 M PBS, pH 7.4, at 10.7 ml/hr, and 3 ml fractions were collected. The total IgE levels and the values of anti-IgE autoantibody were examined in each fraction. Panel A shows the protein elution profile measured at OD 280 nm. Panel B shows the levels of total IgE protein. Panel C shows the levels of anti-IgE autoantibody. Panel D shows the levels of anti-IgE autoantibody after heating the same sample at 56°C for 4 hr.

inhibition study. This anti-IgE autoantibody bound to two different intact human IgE myeloma proteins, but not to other classes of Ig or to heat-denatured IgE protein. After heating at 56°C for 4 hr, the D ϵ 2 antigenicity of the Fc portion of IgE was lost (4). Thus, it is apparent that the anti-IgE autoantibody in atopic dermatitis reacts exclusively with the D ϵ 2 portion of IgE protein.

Williams et al. (5) reported the presence of a naturally occurring IgM class anti-IgE autoantibody in the sera from miscellaneous patients by using the tanned cell hemagglutination technique. We found no evidence of the IgM class anti-IgE autoantibody in our EIA. Inganäs et al. (6) detected an antibody that could bind to both Staphylococcal protein A and IgE in 35% of 79 sera from nonatopic normal individuals and in 71% of 31 sera from patients with atopic asthma. We found much the same evidence in patients with bronchial asthma (1). But no author has reported data regarding the anti-IgE autoanti-

bodies in atopic dermatitis.

According to the gel filtration experiments, we reported that the anti-IgE autoantibody in sera from individuals with bronchial asthma was present not only in monomeric form, but also in the form of an immune complex with self IgE (1). In the sera from those with atopic dermatitis, the anti-IgE autoantibody was also present, mainly as the immune complex form with self IgE.

There are reports concerning the presence of immune complexes in sera from patients with atopic diseases (7–13). Most complexes are considered to be composed of specific IgE and corresponding antigens. Although we cannot completely exclude the possibility that the IgE peak of the large molecular size detected by a gel filtration analysis in this study may be composed of this type of immune complex, it is clear that the anti-IgE autoantibody corresponding to the large m.w. of IgE in the immune complex form is also present.

Brostoff et al. (7) used density gradient ultracentrifugation to detect the IgE immune complex in sera from patients with atopic dermatitis and hay fever. They pointed out the possibility of an anti-IgE immune complex. There are reports concerning low serum complement levels in sera from individuals with atopic dermatitis (14), and the deposition of Ig associated with complements in affected skin (15), which may support the idea of immune complexes in sera from patients with atopic dermatitis.

There is literature on defective cell-mediated immunity in cases of atopic dermatitis (16–24). Included are delayed-type skin unresponsiveness to various antigens (16–20), diminished responsiveness of cultured lymphocytes to mitogens (16–18, 21), depressed concanavalin A-induced suppressor T cell activity (25), and decreased phagocytic capacity and chemotaxis of neutrophils and monocytes (21, 23–25). On the other hand, there are some reports concerning the helper T cell response to allergen (26) and reversible neutrophil chemotaxis (27) in atopic dermatitis. Elliott and Hanifin (28) showed that the impaired responsiveness of lymphocytes to phytohemagglutinin is secondary to some unknown factor in sera from patients with atopic dermatitis.

Although it is not clear whether the dysfunction of cell-mediated immunity in atopic dermatitis is primary or secondary, the findings do correlate with the severity of skin lesions (16–18), which parallels the serum IgE levels (16, 17, 29–32). In addition to mast cells and basophils (33), the Fc receptor for IgE (Fc ϵ R) is present on various kinds of cells (34–42). Melewicz et al. (36) reported increased numbers of monocytes with Fc ϵ R in allergic patients. Spiegelberg et al. (40) found increased numbers of Fc ϵ R-positive lymphocytes in severe atopic disorders. Rouzer et al. (34) noted that mouse peritoneal macrophages responded to IgE immune complexes, and Ito et al. (42) found that the soluble immune complexes composed of human IgE and goat anti-IgE antibody in vitro could inhibit the chemotaxis of human neutrophils.

All of these findings taken together suggest that the impaired cell-mediated immunity in atopic dermatitis with high serum IgE levels might be induced by IgE-anti-IgE immune complexes by a reaction with lymphocytes, macrophages, monocytes, and neutrophils that have receptors for IgE immune complexes.

Most recently, Hassner and Saxon (39) reported that

the IgE immune complexes composed of human IgE and mouse anti-IgE antibody could activate IgE isotype-specific human suppressor T cells for human myeloma IgE synthesis. This may support the idea that the IgE-anti-IgE immune complex plays a significant role as a regulatory factor in the negative feedback mechanism of IgE production, especially in hyper IgE states. Whether or not the IgE-anti-IgE immune complex that we detected can induce IgE-specific suppressor T cells was not elucidated.

In conclusion, we note the existence of an anti-IgE autoantibody and IgE-anti-IgE immune complex in sera from patients with atopic dermatitis. The possible role of the autoantibody and immune complex as modulators of cell-mediated immunity and in the regulation of IgE production, and the participation of an antigen-nonspecific, IgE-mediated mechanism in the pathogenesis of atopic dermatitis need to be given consideration.

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