

IgE autoantibodies in atopic dermatitis – occurrence of different antibodies against the CH3 and the CH4 epitopes of IgE

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Levels of “free” anti-IgE autoantibodies and IgE/anti-IgE immune complexes were measured in the sera of patients with atopic dermatitis before and after treatment, psoriasis patients, and nonatopic controls. In this measurement, we used two monoclonal antibodies with distinct *in vitro* functions (LE 27, BSW 17), directed against the epsilon CH3 and CH4 domains of the IgE Fc-fragment, in a novel immunobinding assay. In patients with atopic dermatitis, elevated levels of “free” anti-IgE antibodies and IgE/anti-IgE immune complexes were detected in comparison to psoriasis patients and controls. In addition, there was a positive correlation between total IgE and the amount of IgE/anti-IgE complexes detected by LE 27 ($r = 0.7$; $P < 0.001$) or BSW 17 ($r = 0.64$; $P < 0.001$) in patients with atopic dermatitis. In contrast, an inverse correlation was observed between total IgE and “free” anti-IgE antibodies ($r = -0.34$; $P \leq 0.05$) in atopic dermatitis. However, serum levels of anti-IgE autoantibodies before and after therapy in patients with atopic dermatitis did not differ, and levels of anti-IgE antibodies did not correlate with clinical severity, as evaluated by an established clinical scoring system. Our data clearly indicate that significantly elevated amounts of anti-IgE antibodies could be observed in patients with atopic dermatitis, which are directed against different epitopes on the IgE molecule. It is tempting to speculate that these autoantibodies exert different effects on IgE-receptor-bearing effector cells and may play an important role in IgE regulation.

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Although several studies of recent years have offered new insights into the immunologic basis of atopic dermatitis (AD), the pathogenesis of the disease is still not clearly understood. Interaction of allergen with IgE-receptor-bearing effector cells, such as Langerhans' cells or mast cells, in concert with a specific alteration of the cytokine profile of T cells associated with an activation of eosinophils, is a characteristic feature of the initiation of atopic inflammation (7, 23).

There is convincing evidence that autoantibodies directed against IgE, first described in 1972, may occur in a variety of inflammatory disorders (31). Accordingly, elevated serum levels of anti-IgE antibodies and the occurrence of IgE/anti-IgE immune complexes have been measured in atopic disorders (1, 3, 9, 11, 16, 17, 19, 21, 27) and the hyper-IgE syndrome (20). It has been reported that these auto-

antibodies may interfere with immunoassay of serum IgE since IgE might be hidden within IgE/anti-IgE immune complexes and, therefore, not be detectable *in vitro* (22, 28). Moreover, it can be demonstrated that anti-IgE antibodies are involved in the modulation of a variety of immune functions. Accordingly, it has been shown that anti-IgE autoantibodies modify the binding of IgE to IgE-receptor-bearing cells (24). It has also been shown that anti-IgE autoantibodies may induce mediator release from human basophils, tissue mast cells, and bone-marrow cells *in vitro* (3, 13). In contrast, anti-IgE antibodies failed to trigger histamine release from blood basophils, suggesting that different types of autoantibodies exist and can either block or induce histamine release (6, 24). In addition, anti-IgE antibodies may have the capacity to modulate IgE synthesis (26). Recently, human anti-IgE antibodies have been isolated by

repertoire cloning with phage display libraries (29). However, the pathophysiologic role of natural anti-IgE autoantibodies and their relation to disease activity in atopic diseases have not been clearly elucidated.

In the present study, for further evaluation of the relevance of anti-IgE autoantibodies, serum levels of "free" and complexed anti-IgE autoantibodies were determined, by means of monoclonal antibodies against different epitopes of the IgE molecule, in a novel immunobinding assay in patients with AD during therapy, and compared with those of patients suffering from psoriasis, an inflammatory skin disorder of distinct pathogenesis, as well as with those of normal nonatopic controls.

Material and methods

Patients and controls

Nineteen patients with moderate to severe AD ($\geq 25\%$ of body surface area involved) were examined twice in a follow-up study before and after an interval of treatment (2 weeks in 11 patients, 3 weeks in eight patients). The diagnosis was established according to the criteria of Hanifin & Rajka (4). In addition, 15 patients with extensive plaque-type psoriasis with $\geq 25\%$ body surface involvement and 13 healthy controls without any history or laboratory findings of atopy were included in the study (Table 1).

Clinical scoring system

Before and after successful treatment, the clinical severity of the disease in each patient was determined according to an established scoring system described by Czech et al. (2). Briefly, the total score consisted of ratings for 10 severity criteria and 10 topographic sites. The most severely affected area was chosen for evaluating each of the severity criteria (erythema, edema, vesicles, crusts, excoriations, papules, scales, lichenification, pruritus, and loss of sleep), which were scored from 0 (no lesion) to 6 (extremely severe). The topographic items (feet, knees, legs, hands, arms, face, scalp, buttocks, and anterior and posterior aspects of the trunk) were scored from 0 to 3, according to the extent of skin lesions. Clinical assessment was performed indepen-

dently by two different investigators without significant differences.

Therapeutic modalities

Various therapeutic regimens have been employed to treat AD patients, including topical and systemic glucocorticosteroid therapy, UVA/UVB irradiation, and high-dose-UVA1 phototherapy (12). Treatment of patients in hospital lasted for intervals in a range of 9–28 days.

Collection of serum samples

A volume of 10 ml of peripheral blood was collected by venipuncture in patients at the indicated time points and once in healthy controls, and it was kept at room temperature for 60 min, and then at 4°C for an additional 30 min. Centrifugation was performed at 850 g for 10 min at 4°C, and the serum was aspirated and frozen at –70°C until testing (8).

Determination of total and specific IgE

Total IgE was determined in the sera of patients and control subjects with the CAP IgE FEIA (Kabi-Pharmacia, Freiburg, Germany). The presence of specific IgE was screened by CAP FEIA multidisk sx1 (Kabi-Pharmacia, Freiburg, Germany). The following allergens were coupled to multidisk sx1: timothy, cultivated rye, common silver birch, mugwort, cat, *Cladosporium herbarum*, and *Dermatophagoides pteronyssinus*. The results were expressed as negative or positive. The result was "positive" if specific IgE could be detected against at least one of the allergens listed above.

Detection of IgG anti-IgE autoantibodies and IgE/anti-IgE immune complexes in serum

Anti-IgE antibodies in "free" form, as well as in immune complexes of IgE and anti-IgE, were measured by a novel dot immunobinding assay, as previously described (28). Natural anti-IgE antibodies capable of directly recognizing purified solid-phase IgE were termed "free" anti-IgE antibodies. IgE/anti-IgE immune complexes were measured in human serum by dotting the murine monoclonal antihuman IgE antibodies BSW 17 or LE 27, respectively, onto nitrocellulose as solid phase. These antibodies are directed against different epitopes of the IgE Fc fragment, but both are of the murine IgG1 isotype. The major difference between the biologic function of the two antibodies is that LE 27 is a potent anaphylactic antibody, while BSW 17 does not trigger histamine or leukotriene release from human basophils (10, 15).

Table 1. Characterization of patients and control subjects

Disease	No. of patients	Sex	Mean age (yr)	Age range (yr)	Multidisk sx1
Atopic dermatitis	19	9 M 10 F	26	18–41	18 P/1 N
Psoriasis	15	9 M/6 F	36	21–54	3 P/12 N
Controls	13	7 M/6 F	27	19–40	0 P/13 N

F, female; M, male; P, positive; N, negative.

Statistical evaluations

The differences in clinical severity scores, IgE, "free" anti-IgE, and IgE/anti-IgE immune complexes before and after treatment in patients with AD were evaluated with the Wilcoxon test. Differences in IgE, "free" anti-IgE, and IgE/anti-IgE immune complexes between patients and controls were analyzed by the Mann-Whitney U-test. The correlation between clinical scores and laboratory data was calculated by Spearman's rank correlation and tested for statistical significance.

Results

Clinical severity score

Clinical examination of patients with AD before and after therapy indicated that clinical improvement of the skin symptoms was accompanied by a significant decrease in clinical score points (Table 2).

Immunologic parameters

IgE. Patients with AD showed significantly higher levels of serum IgE than controls. One patient showed serum IgE levels within the normal range (≤ 100 kU/l) with a negative sxl-test. There was no significant difference before and after treatment. In patients with chronic plaque-type psoriasis, significantly elevated levels of serum IgE as compared with controls could be measured. However, only three patients showed elevated levels of serum IgE above the normal range (≥ 100 kU/l) associated with a positive sxl-test without clinical signs of atopic disease. Most of the 12 patients showed serum IgE levels within the normal range (Table 2).

"Free" anti-IgE. Significantly elevated levels of "free" anti-IgE autoantibodies could be detected in sera of patients with AD as compared to controls (Fig. 1). The patients with normal IgE serum levels also had low levels of "free" anti-IgE in serum. In addition, no difference in "free" anti-IgE autoantibodies in the

Table 2. Serum IgE levels in patients with atopic dermatitis (AD) before and after therapy, patients with psoriasis vulgaris, and nonatopic controls

IgE (kU/l)	Atopic dermatitis		Psoriasis	Controls
	Before	After		
Geometric mean	2821**	2458 ^(NS)	56*	24
Median	2760	2310	54	18
Range	22–31200	20–24650	4–1887	5–95

* $P \leq 0.05$ as compared with controls; ** $P \leq 0.001$ as compared with patients before therapy.

^(NS) There was no significant difference before and after therapy in patients with AD.

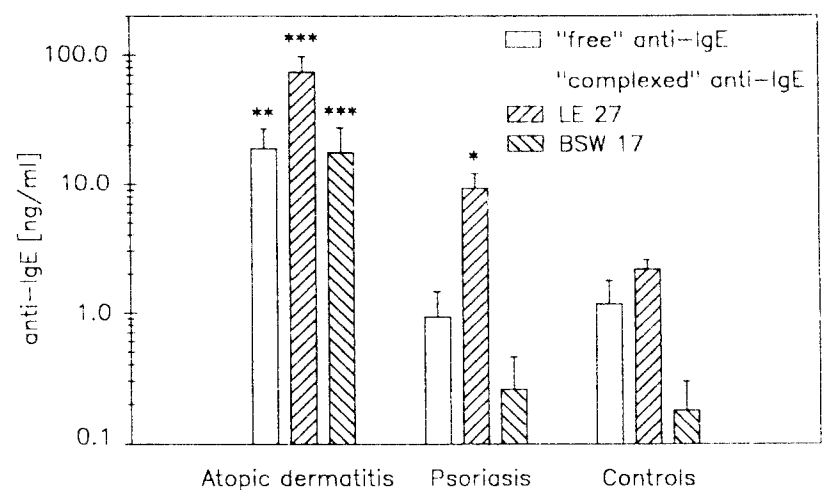


Fig. 1. Detection of "free" and "complexed" anti-IgE autoantibodies. "Complexed" anti-IgE was measured with different anti-IgE antibodies, as described in Material and methods.

sera of AD patients before and after treatment, despite marked clinical improvement, could be detected (Table 3). In patients with psoriasis, there was no significant difference in serum levels of "free" anti-IgE as compared to controls.

IgE/IgG anti-IgE immune complexes. In patients with AD, significantly elevated amounts of IgE/IgG anti-IgE immune complexes detected by monoclonal antibody LE 27 and BSW 17 could be measured as compared with controls. There was no difference in levels of complexed IgE/anti-IgE autoantibodies in patients with AD before and after treatment (Table 3). Interestingly, IgE/anti-IgE immune complexes could be measured in low amounts also in the

Table 3. Clinical severity score and anti-IgE autoantibodies in patients with AD before and after therapy

Parameters	AD patients	
	Before	After
Clinical severity score (points)		
Geometric mean	54	21*
Median	57	24
Range	21–73	4–46
"Free" anti-IgE (ng/ml)		
Geometric mean	19	25 ^(NS)
Median	3	4
Range	0–148	0–211
"Complexed" anti-IgE, LE 27 (ng/ml)		
Geometric mean	74	69 ^(NS)
Median	24	26
Range	2–379	4–343
"Complexed" anti-IgE, BSW 17 (ng/ml)		
Geometric mean	18	16 ^(NS)
Median	2	2
Range	0–166	0–169

* $P \leq 0.001$ as compared with patients before therapy. ^(NS) There was no significant difference before and after therapy in patients with AD.

sera of controls (Fig. 1). In patients with psoriasis, significantly elevated amounts of complexed anti-IgE autoantibodies detected with monoclonal antibody LE 27 could be measured as compared with controls. These immune complexes could be detected in the sera of patients with elevated IgE serum levels and a positive sxl-test. In contrast, there was no difference in the amount of IgE/anti-IgE immune complexes detected by antibody BSW 17 in the sera of patients with psoriasis and of controls (Fig. 1).

Correlation between anti-IgE autoantibodies and IgE in serum. In the 66 assessments in the 34 patients and 13 controls investigated, there was a significant positive correlation between IgE and IgE/anti-IgE immune complexes detected with monoclonal antibody LE 27 ($r = 0.81$; $P < 0.0001$), as well as IgE and IgE/anti-IgE immune complexes detected with monoclonal antibody BSW 17 ($r = 0.69$; $P \leq 0.0001$) (Figs. 2 and 3). In addition, a significant correlation could be observed between the level of immune complexes detected by BSW 17 and LE 27 ($r = 0.76$; $P \leq 0.0001$) (data not shown). There was no correlation between "free" anti-IgE autoantibodies and serum IgE (data not shown). There was a significant positive correlation between IgE and IgE/anti-IgE immune complexes detected with monoclonal antibodies LE 27 ($r = 0.7$; $P \leq 0.001$) and BSW 17 ($r = 0.69$; $P \leq 0.001$) when the 38 assessments in patients with AD before and after treatment were evaluated separately. In addition, an inverse correlation could be found between "free" anti-IgE autoantibodies and serum IgE ($r = -0.34$; $P \leq 0.05$) (data not shown).

Correlation between anti-IgE autoantibodies and clinical severity in AD. There was no significant correlation between "free" or complexed anti-IgE auto-

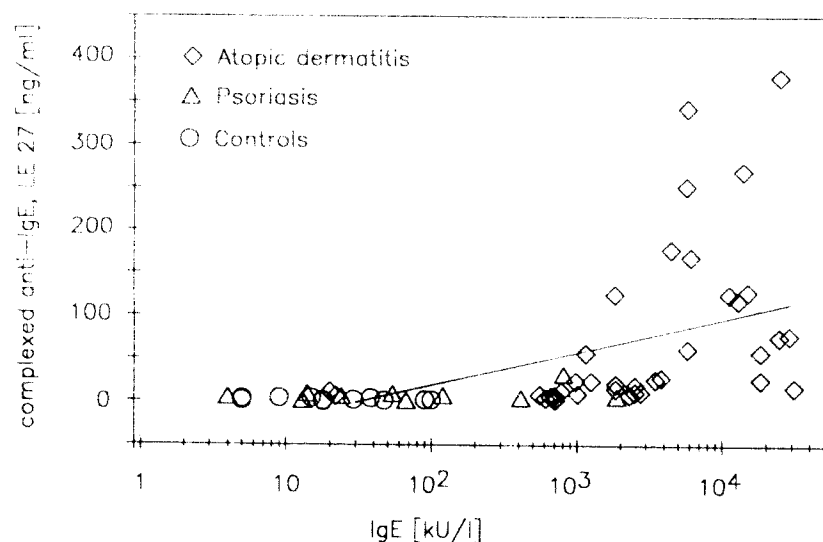


Fig. 2. Correlation between serum IgE and IgE/anti-IgE immune complexes detected by monoclonal anti-IgE antibody LE 27 in patients with atopic dermatitis ($\diamond$), psoriasis ($\triangle$), and controls ($\circ$); total assessments: $n = 66$; $r = 0.81$; $P \leq 0.0001$.

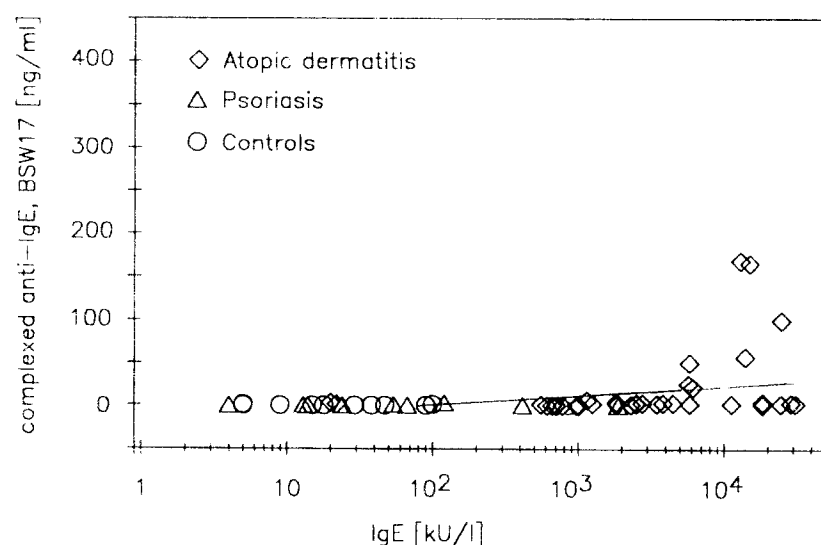


Fig. 3. Correlation between serum IgE and IgE/anti-IgE immune complexes detected by monoclonal anti-IgE antibody LE 27 in patients with atopic dermatitis ($\diamond$), psoriasis ($\triangle$), and controls ($\circ$); total assessments: $n = 66$; $r = 0.69$; $P \leq 0.0001$.

antibodies detected by the two different monoclonal antibodies BSW 17 and LE 27 and the clinical score (data not shown).

Discussion

The present study showed that anti-IgE autoantibodies are elevated in the sera of patients with AD and directed against different epitopes of the IgE molecule. Moreover, these antibodies occur both as "free" autoantibodies and in immune complexes with IgE. However, autoantibodies against IgE did not correlate with disease activity in AD.

In contrast to immunoglobulin E, which is elevated in serum in most patients suffering from AD and directed against environmental allergens, the relevance of anti-IgE autoantibodies is still obscure (18, 25). This study demonstrated that, besides IgE, IgG anti-IgE autoantibodies, either as "free" antibodies or bound within IgE/anti-IgE immune complexes, also occur in significantly higher amounts in the sera of patients with AD than in patients with psoriasis or controls. Although the occurrence of anti-IgE autoantibodies has been demonstrated previously in various pathologic conditions related to atopy and in arthritis, and occasionally these autoantibodies occur naturally, our data are unique in several aspects (1, 16, 17, 21, 31).

In contrast to AD patients, patients with psoriasis, an inflammatory skin disease of distinct pathogenesis, did not show elevated levels of "free" anti-IgE autoantibodies or anti-IgE-containing immune complexes detected by antibody LE 27. There was a significant elevation of immune complexes detected by antibody BSW 17. However, elevation could be observed only in patients with an elevated serum IgE level associated with the presence of allergen-specific IgE as a sign of atopic disposition. Therefore, production of anti-IgE is more likely to depend on the

presence of IgE and atopy than purely on the presence of acute or chronic inflammation.

This result is also of technical interest. Both the murine antibodies LE 27 and BSW 17 are of the IgG1 isotype. By the sandwich assay for detecting IgE in complexes, it is known that some of the signal can also be attributed to panspecific anti-IgG antibodies that also react with murine monoclonal antibodies. Thus, these data show that the observed differences cannot be attributed to cross-reaction with panspecific anti-IgG antibodies. Previously, we have also reported that there was no correlation between IgE and anti-IgE antibodies in a group of patients comprising normal and asthmatic children with only slightly elevated IgE levels. Here it was of interest that a positive correlation was found, especially in the donors with AD who showed elevated serum IgE levels, but no correlation was found if the psoriasis patients or controls were analyzed independently (22).

However, the present study demonstrated, by an established and elaborate clinical scoring system, that anti-IgE autoantibodies did not correlate with disease activity in AD. It is well known that corticosteroids, by exerting immunosuppressive effects, may have the capacity to inhibit the synthesis of immunoglobulins. However, the finding of unchanged anti-IgE levels in the sera of patients despite clinical improvement may be due to the short duration of clinical observation (2–3 weeks) of the patients and the well-known half-life of IgG antibodies of about 3 weeks.

In contrast, recent reports have demonstrated that measurement of eosinophil cationic protein is a suitable parameter for monitoring disease activity in AD (2, 5).

As shown by a novel immunobinding assay using monoclonal antibodies against anti-IgE as catching antibodies in the solid phase of the immunoassay, the data provide clear evidence that major amounts of naturally occurring antibodies against the IgE molecule are bound as IgE-IgG anti-IgE immune complexes. Moreover, there was a significant positive correlation between serum IgE and IgG anti-IgE immune complexes, indicating an affinity for anti-IgE autoantibodies in the formation of immune complexes, an affinity which may cause interference with diagnostic IgE determination, as previously described (28). In contrast, there was no relevant correlation between serum IgE and "free" anti-IgE autoantibodies. Different amounts of IgE-IgG anti-IgE immune complexes could be measured with the monoclonal anti-IgE antibodies BSW 17 and LE 27, which are directed against different epitopes of the IgE molecule, namely, the epsilon CH3 and CH4 domains, respectively. Therefore, we suggest that different anti-IgE autoantibodies exist and are di-

rected against the epsilon CH3 and CH4 domains. The fact that the amount of immune complexes detected by monoclonal antibody LE 27 is significantly higher than the amount detected by BSW 17 shows that naturally occurring antibodies in the serum of patients with AD are mainly of the BSW 17 type and are directed against the epsilon CH3 domain. However, the present study cannot exclude the occurrence of IgE autoantibodies against epitopes besides the CH3 or CH4 domain of the IgE molecule. Recently, we have provided further support for the method of detecting domain-specific anti-IgE autoantibodies. Accordingly, human anti-IgE autoantibodies could be identified which had been mapped by Western blotting against a series of recombinant ϵ -domain peptides. Antibodies specific for all ϵ -domains were detected (14).

The functional relevance of IgE autoantibodies *in vivo* is still unclear. Anti-IgE autoantibodies may be of functional relevance since induction of a wheal-and-flare reaction in several urticarial syndromes could be observed (3). Moreover, it has been shown in an animal model that anti-idiotypic antibodies specific for IgE idiotype can induce mediator release from IgE-sensitized mast cells *in vivo* (30). Monoclonal antibodies used in the present study were shown to have distinct functional properties. Accordingly, LE 27 has been shown to trigger histamine release from human leukocytes *in vitro*, whereas BSW 17 inhibits binding of IgE to the low-affinity IgE receptor Fc ϵ RII and does not release histamine (10, 15). Therefore, it is tempting to speculate that high levels of anti-IgE autoantibodies may be relevant in the pathogenesis of IgE-mediated immune reactions in AD.

In summary, the present data indicate that autoantibodies against different epitopes of IgE occur in patients with AD; however, the occurrence of these autoantibodies is not correlated with the disease activity. Therefore, further studies are needed to clarify the functional role of these antibodies in the pathogenesis of AD.

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