

Short communication

Anti-Fc ϵ RI α serum autoantibodies in different subtypes of urticaria

Background: In recent years, a histamine-releasing anti-Fc ϵ RI α autoantibody has been demonstrated in about one-third of patients with chronic urticaria. However, its clinical significance is still unclear. The objective was to detect a possible correlation between the occurrence of the anti-Fc ϵ RI α autoantibody and the clinical type or cause of urticaria.

Methods: Sera from 66 consecutively seen in- and outpatients with various types of urticaria and five healthy controls were examined for the presence of anti-Fc ϵ RI α autoantibodies with a sandwich ELISA technique. In addition, basophil histamine release was studied in 13 autoantibody-positive sera.

Results: Anti-Fc ϵ RI α autoantibodies were found in 17/48 patients with chronic urticaria, in 2/4 with angioedema, in 1/2 with urticarial vasculitis, and in 2/11 with dermatographic urticaria. However, no anti-Fc ϵ RI α autoantibodies were detected in acute, cold, or delayed-pressure urticaria; in urticaria pigmentosa; or in normal controls. Of all chronic urticaria patients, 22 were classified as idiopathic since no underlying cause could be found. Of this group, seven were seropositive for anti-Fc ϵ RI α . However, anti-Fc ϵ RI α was also found in patients who went into remission after treatment of identified causes; namely, in one with type I allergy, one with drug intolerance, one with *Helicobacter* infection, and six with food intolerance. The autoantibody was also detected in 2/4 patients with associated autoimmune diseases. Functional activity was shown in basophil histamine release in 3/4 autoantibody-positive sera of patients with chronic idiopathic urticaria and in 4/6 autoantibody-positive sera of patients who went into remission after the treatment of underlying causes.

Conclusions: These data confirm that anti-Fc ϵ RI α autoantibodies in urticaria are mostly found in chronic urticaria. Furthermore, their detection independently of the apparent cause of the urticaria suggests that as yet unidentified mechanisms must be operative, possibly related to the chronic inflammatory process and/or individual predispositions that favor their induction.

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The pathogenesis of urticaria is largely unclarified, although mast-cell-dependent mediator release is generally accepted to be the common denominator of the underlying mechanisms of the diverse subtypes of the disease (1). In contrast to generally held opinions, specific IgE sensitization is rare, and, instead, acute urticaria often arises in association with viral diseases (2, 3), and pseudoallergens in drugs and food have been shown to elicit the reactions in more than half of chronic urticaria patients (4). Chronic urticaria also encompasses whealing reactions in the framework of the so-called physical urticaria, which is elicited on contact of the skin with mechanical stimuli or electromagnetic waves (reviewed in Henz et al. [1]).

Major advances in the understanding of the patho-

genesis of urticaria were made in recent years with the demonstration that, in about 60% of patients with chronic idiopathic urticaria, whealing reactions can be elicited on injection of the patient's own serum (5). Further investigations showed that in about 23% of these patients, an autoantibody to the α -chain of the high-affinity IgE receptor (Fc ϵ RI α) was found to induce mediator release from normal donors' blood basophils and skin mast cells (6–9). These findings were confirmed independently by other groups (10–13). Furthermore, the autoantibodies were also identified in several types of autoimmune disease (14) as well as in atopy and healthy individuals (15).

Reasons for the development of functional anti-Fc ϵ RI α antibodies in a subgroup of patients with chronic urticaria and their potential disease-initiating or sustaining significance are currently unclear. The therapeutic implications have so far been unclarified (16).

Abbreviations. Fc ϵ RI: α chain of the high-affinity IgE receptor; MHC: major histocompatibility complex; scOD: specific corrected optical density; TNF: tumor necrosis factor.

Since chronic urticaria encompasses a broad spectrum of clinical subtypes and eliciting causes, we have tried to shed further light on the pathogenetic significance of the anti-Fc ϵ RI α antibodies in chronic urticaria by examining routinely collected sera from a group of patients with diverse types of urticaria. The data show that the occurrence of the anti-Fc ϵ RI α autoantibodies is also found in patients whose disease responded to cause-related treatment.

Material and methods

Venous blood was collected routinely for diagnostic purposes from consecutively presenting urticaria patients at the in- and outpatient departments of dermatology of the Charité in Berlin, Germany, over a 1-year period. After clotting, the sera were stored in aliquots at -60°C . Aliquots were shipped on dry ice and in one lot for anti-Fc ϵ RI α autoantibody analysis to the department of dermatology, University of Vienna Medical School, Vienna, Austria.

The diagnosis of different types and causes of urticaria was made on the basis of a thorough history and physical examination, appropriate provocation and laboratory tests, and remission of the disease on elimination of implicated causes, as previously detailed (1, 4, 17). Briefly, chronic urticaria was defined as lasting for at least 6 weeks, with a chronic continuous or intermittent overall course. To diagnose pseudoallergies, patients had to improve on a diet free of preservatives, colorings, and natural aromas, with recurrence of symptoms on blinded oral provocation. The diagnosis of dermographic and delayed-pressure urticaria was confirmed with an immediate reaction on application of a shearing pressure with a dermatographometer and a deep wheal 4–8 h after application of static pressure with a special device, respectively, as previously described (1). For the diagnosis of urticaria vasculitis, leukocytoclastic vasculitis had to be present on lesional histology (1).

ELISA measurements were conducted as previously

Table 1. Serum antibody reactivity in patients with different types of urticaria

Clinical type of urticaria	Number tested	Number anti-Fc ϵ RI α positive§	
		+	++
Acute urticaria	1	0	0
Chronic recurrent urticaria	48	10	7
Angioedema	4	1*	1+
Urticarial vasculitis	2	0	1
Dermographic urticaria	11**	2+	0
Delayed-pressure urticaria	1	0	0
Cold urticaria	1	0	0
Urticaria pigmentosa	1	0	0
Normal controls	5	0	0

* This patient suffered also from associated chronic recurrent urticaria.

** Two patients suffered also from associated chronic recurrent urticaria.

+ No associated chronic recurrent urticaria.

§ +: moderate (scOD titer 41–90); ++: strong reactivity of sera (scOD titer >90) (8).

Table 2. Serum autoantibody reactivity in chronic urticaria patients with different underlying causes, as proven by provocation tests and remission on omission or after specific treatment targeted at putative cause

Cause of chronic urticaria	Number tested	Number anti-Fc ϵ RI α positive§	
		+	++
Type I allergy	2	0	1 ^a
Drug intolerance	4	0	1 ^b
Food intolerance ^c	17	3	3
<i>Helicobacter pylori</i>	1	0	0
Intestinal candidosis	1	0	0
Association with autoimmune diseases	2	1 ^d	1 ^e
Idiopathic	22	4	3

^a To latex and cross-reacting foods.

^b To paracetamol.

^c Proven by oral provocation to food additives and natural aromas and remission on diet avoiding these agents (14).

^d Hashimoto's thyroiditis.

^e Vasculitis and rheumatoid arthritis.

§ +: moderate (scOD titer 41–90); ++: strong reactivity of sera (scOD titer >90) (8).

described (14). Sera with a specific corrected optical density (scOD) of <40 were classified as negative, those with an scOD of 41–90 as moderately (+) positive, and those with an scOD of >90 as strongly (++) positive. Basophil histamine release was studied as previously described (7), at least two different donors and normal as well as IgE-stripped cells being used.

Results

As with most types of urticaria, there was a predominance of females (68.2%) over males in the present patient population. However, more males (47.6%) than females (31.1%) had detectable autoantibodies in their serum, although strong reactivity was found in more females (8/18) than males (1/8).

When examined for anti-Fc ϵ RI autoantibodies in different types of urticaria (Table 1), most sera were found to be positive in chronic recurrent urticaria, with slightly more patients exhibiting moderately than markedly elevated titers. Anti-Fc ϵ RI α autoantibodies were also detected in two patients with angioedema, irrespective of the presence of associated chronic urticaria, in one of two patients with urticarial vasculitis, and in two patients with dermographic urticaria in the absence of chronic urticaria.

In 55.1% of the patients with chronic recurrent urticaria, excluding physical urticaria, an eliciting or probably causative agent could be identified (Table 2).

Table 3. Investigation of basophil histamine releasability in anti-Fc ϵ RI α -positive chronic urticaria patients with different underlying causes

Cause of chronic urticaria (n)	Positive basophil histamine-release test
Food intolerance (5)	3/5
<i>Helicobacter pylori</i> (1)	1/1
Idiopathic (4)	3/4

Among these, anti-Fc ϵ RI α autoantibody reactivity was found in the two patients with associated autoimmune phenomena, and in one patient each with type I allergy and an intolerance reaction to the nonsteroidal anti-inflammatory drug paracetamol, respectively. Furthermore, elevated anti-Fc ϵ RI α autoantibody titers were detected in 6/17 patients in whom natural aromas and food additives were identified as eliciting and sustaining causes of their chronic urticaria.

Seven sera were also positive among the remaining 22 patients with so-called idiopathic urticaria where no obvious cause of the urticaria could be found.

In order to check the functional activity of these autoantibodies, 13 sera of chronic urticaria patients were tested for *in vitro* basophil-releasing capacity. Exactly 3/4 autoantibody-positive sera of patients with chronic idiopathic urticaria and 4/6 autoantibody-positive sera of patients who went into remission after the treatment of underlying causes showed histamine-releasing activity (Table 3).

Discussion

The present findings from a sizable number of routinely screened urticaria patients confirm previously published data on the incidence of anti-Fc ϵ RI α autoantibodies in about one-third of patients with chronic urticaria (7–14). They show also that the antibodies are found not only in patients with idiopathic urticaria, but also in those with obvious eliciting agents, as exemplified by the patient who suffered from IgE-dependent combined latex and fruit allergy, and by the patients with proven intolerance to paracetamol or food ingredients. The occurrence of the autoantibodies in chronic urticaria patients with other associated autoimmune processes and in the patient with urticarial vasculitis is particularly interesting since it suggests that the development of the anti-Fc ϵ RI α antibodies may be favored in patients with coexisting autoimmune diseases. The increased incidence of markedly elevated anti-Fc ϵ RI α autoantibody titers in women also fits the known predominance of females over males in the development of autoimmune diseases.

From the present data, the mechanisms inducing

parts of the Fc ϵ RI α -chain to become an auto-immunologic target in seropositive urticaria patients remain unclear. In general, urticaria is not associated with increased IgE levels or atopy (1). Furthermore, patients with the anti-Fc ϵ RI α autoantibody have even lower serum IgE levels than the autoantibody-negative patients (18). On the other hand, TNF- α is upregulated in either the lesional and nonlesional skin or in the serum of patients with all types of urticaria, together with other proinflammatory and immunomodulatory cytokines, as well as with diverse adhesion molecules, including MHC class II molecules (19–23). The chronic upregulation of these proinflammatory and immunomodulatory molecules may favor the development of autoimmune phenomena in predisposed patients. An increased severity of urticaria symptoms in the patients with the anti-Fc ϵ RI α autoantibodies (18) would also suggest this possibility, although the intensity of the inflammatory infiltrate does not seem to be of significance (24).

The present study also shows that the autoantibody-positive sera contain histamine-releasing capacity, suggesting functional autoantibodies (Table 3). Since the occurrence of the autoantibodies was independent of the underlying cause of the disease or state of disease activity, a possible secondary rather than an initiating nature of the autoantibodies in urticaria is indicated. A possible explanation could also be the demand for cofactors required for an activation *in vivo*. A similar situation is found in different urticaria subtypes, such as exercise-induced urticaria and anaphylaxis, where in some patients an IgE-dependent allergen leads to clinically significant mast-cell degranulation only when a second stimulus, such as exercise, is present.

Final conclusions regarding the possible mechanisms of action involved in the generation of the Fc ϵ RI α autoantibodies, as well as their clinical significance, will have to await further studies. In particular, analysis of the autoantibodies in a sizable group of patients suffering from acute urticaria, as well as in the same patients on progression to chronic urticaria, may help to clarify whether the autoantibodies are disease initiating or not, since, by definition, all chronic urticaria must start as acute urticaria.

References

1. HENZ BM, ZUBERBIER T, GRABBE J, MONROE E. Urticaria – clinical, diagnostic and therapeutic approaches. Berlin: Springer, 1998.
2. ZUBERBIER T, IFFLÄNDER J, SEMMLER C, CZARNETZKI BM. Acute urticaria – clinical aspects and therapeutic responsiveness. *Acta Derm Venereol* 1996;**76**:295–297.
3. MORTUREUX P, LÉAUTÉ-LABRÈZE C, LEGRAIN-LIFERMANN V. Acute urticaria in infancy and early childhood. A prospective study. *Arch Dermatol* 1998;**134**:319–323.
4. HENZ BM, ZUBERBIER T. Most chronic urticaria is food-dependent, and not idiopathic. *Exp Dermatol* 1998;**7**:139–142.
5. GRATTAN CEH, BOON AP, EADY RAJ, WINKELMANN RK. The pathology of the autologous serum skin test response in chronic urticaria resembles IgE-mediated late-phase reactions. *Int Arch Allergy Appl Immunol* 1990;**93**:198–204.

6. GRATTAN CE, FRANCIS DM, HIDE M, GREAVES WM. Detection of circulating histamine releasing autoantibodies with functional properties of anti-IgE in chronic urticaria. *Clin Exp Allergy* 1991;**21**:221–224.
7. HIDE M, FRANCIS DM, GRATTAN CE, HAKIMI J, KOCHAN JP, GREAVES MW. Autoantibodies against the high-affinity IgE receptor as a cause of histamine release in chronic urticaria. *N Engl J Med* 1993;**328**:1599–1604.
8. HIDE M, FRANCIS DM, GRATTAN CE, BARR RM, WINKELMANN RK, GREAVES MW. The pathogenesis of chronic idiopathic urticaria: new evidence suggests an auto-immune basis and implications for treatment. *Clin Exp Allergy* 1994;**24**:624–627.
9. NIIMI N, FRANCIS DM, KERMANI F, et al. Dermal mast cell activation by autoantibodies against the high affinity IgE receptor in chronic urticaria. *J Invest Dermatol* 1996;**106**:1001–1006.
10. FIEBIGER E, MAURER D, HOLUB H, et al. Serum IgG autoantibodies directed against the α chain of Fc ϵ RI: a selective marker and pathogenetic factor for a distinct subset of chronic urticaria patients? *J Clin Invest* 1995;**96**:2606–2612.
11. FIEBIGER E, STINGL G, MAURER D. Anti-IgE and anti-Fc ϵ RI autoantibodies in clinical allergy. *Curr Opin Immunol* 1996;**8**:784–789.
12. TONG LJ, BALAKRISHNAN G, KOCHAN JP, KINET J-P, KAPLAN AP. Assessment of autoimmunity in patients with chronic urticaria. *J Allergy Clin Immunol* 1997;**99**:461–465.
13. FERRER M, KINET J-P, KAPLAN AP. Comparative studies of functional and binding assays for IgG anti-Fc ϵ RI α (α -subunit) in chronic urticaria. *J Allergy Clin Immunol* 1998;**101**: 672–676.
14. FIEBIGER E, HAMMERSCHMIDT F, STINGL G, MAURER D. Anti-Fc ϵ RI autoantibodies in autoimmune-mediated disorders. Identification of a structure-function relationship. *J Clin Invest* 1998;**101**:243–251.
15. HORN MP, GERSTER T, OCHSENBERGER B, et al. Human anti-Fc ϵ RI α autoantibodies isolated from healthy donors cross-react with tetanus toxoid. *Eur J Immunol* 1999;**29**:1139–1148.
16. TOUBI E, BLANT A, KESSEL A, GOLAN TD. Low-dose cyclosporin A in the treatment of severe chronic idiopathic urticaria. *Allergy* 1997;**52**:312–316.
17. ZUBERBIER T, CHANTRAINE-HESS S, HARTMANN K, CZARNETZKI BM. Pseudoallergen-free diet in the treatment of chronic urticaria. *Acta Derm Venereol (Stockh)* 1995; **75**:484–487.
18. SABROE RA, SEED PT, FRANCIS DM, BARR RM, BLACK AK, GREAVES MW. Chronic idiopathic urticaria: comparison of the clinical features of patients with and without anti-Fc ϵ RI or anti-IgE autoantibodies. *J Am Acad Dermatol* 1999;**40**:443–450.
19. KANO Y, ORIHARA M, SHIOHARA T. Cellular and molecular dynamics in exercise-induced urticarial vasculitis lesions. *Arch Dermatol* 1998;**134**:62–67.
20. HAAS N, IWEN W, GRABBE J, UCHANSKA-ZIEGLER B, CZARNETZKI BM. MHC class II expression in different forms of urticaria. *Int Arch Allergy Immunol* 1996;**109**:177–182.
21. ZUBERBIER T, SCHADENDORF D, HAAS N, HARTMANN K, HENZ BM. Enhanced P-selectin expression in chronic and dermographic urticaria. *Int Arch Allergy Clin Immunol* 1997;**114**:86–89.
22. HAAS N, SCHADENDORF D, HENZ BM. Differential endothelial adhesion molecules in immediate and delayed urticarial whealing reactions. *Int Arch Allergy Immunol* 1998;**115**:210–214.
23. HERMES B, PROCHAZKA A-K, HAAS N, JURGOVSKY K, STICHERLING M, HENZ BM. Upregulation of tumor necrosis factor α and interleukin-3 expression in lesional and uninvolved skin in different types of urticaria. *J Allergy Clin Immunol* 1999;**103**:307–314.
24. SABROE RA, POON E, ORCHARD GE, et al. Cutaneous inflammatory cell infiltrate in chronic idiopathic urticaria: comparison of patients with and without anti-Fc ϵ RI or anti-IgE autoantibodies. *J Allergy Clin Immunol* 1999;**103**:484–493.