

Chronic spontaneous urticaria: an autoimmune disease? A revision of the literature

Gabriele Di Lorenzo · Maria Stefania Leto-Barone ·
Simona La Piana · Aurelio Seidita ·
Giovam Battista Rini

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Abstract The cause of chronic spontaneous urticaria has been an enigma for decades, but the recognition of functional autoantibodies in some patients with the spontaneous chronic urticaria has opened up a new concept of autoimmune urticaria. Clinical and laboratory features are in keeping with an autoimmune aetiology for many patients with otherwise inexplicable disease, but there is still debate about the importance of functional autoantibodies in the disease pathogenesis, how to test them and the clinical implications for treatment and prognosis. This review will look at the evidence for there being an autoimmune subset of urticaria, the strengths and weaknesses of the available tests in current use.

Keywords Urticaria · Histamine-releasing autoantibodies · Autologous serum skin test · Basophils

Introduction

The term ‘idiopathic’, today named as ‘spontaneous’, has been applied to chronic urticaria for many decades to describe the perplexing paradox of a chronic disease that in many respects behaves like an allergic skin reaction with histamine-mediated symptoms but for which no allergic

trigger can be found [1]. Besides, immediate hypersensitivity may be a cause of acute urticaria lasting for days, but clinical experience indicates that allergy is probably never the cause of continuous daily urticaria lasting for weeks or more. It has been recognized for many years that some patients with chronic urticaria have a reproducible physical trigger that reliably induces wheals, angioedema or both. These patients have traditionally been distinguished from those with chronic ‘spontaneous’ urticaria even though the cause of physical urticaria remains unknown [1, 2]. A few others can be shown by skin biopsy to have an underlying small vessel vasculitis, presenting with urticaria rather than palpable purpura [1, 2]. Aggravating factors of chronic ‘spontaneous’ urticaria are well known to patients, including heat, viral infections, some medications (notably non-steroidal anti-inflammatories) and light pressure of clothes, but these are not causes of the condition [3]. Debate about whether dietary pseudoallergens and chronic infections, such as *Helicobacter pylori*, are true causes of chronic continuous urticaria or operate as super-imposed aggravating factors in patients who otherwise have an endogenous disease is not fully resolved [3, 4].

What is becoming increasingly certain though is that the term ‘spontaneous’ is becoming superseded by persuasive immunological explanations for the previously inexplicable. This has led to difficulties with nomenclature and classification of urticaria because accepting the term autoimmune urticaria implies that the old aetiological term ‘spontaneous’ can not be used for the same patient. It is for this reason that emphasis has been given to clinical classifications of urticaria that rely on the clinical behaviour of the disease rather than aetiology (Table 1). The term ‘spontaneous’ used in the EAACI guidelines and embraces all patients presenting with continuous spontaneous wheals, with or without angioedema, whether the course

G. Di Lorenzo (✉) · M. S. Leto-Barone · A. Seidita ·
G. B. Rini
Dipartimento di Medicina Interna e Specialistica (DIMIS),
Università degli Studi di Palermo, Via del Vespro,
141, 90127 Palermo, Italy
e-mail: gabriele.dilorenzo@unipa.it

S. La Piana
Dipartimento di Biopatologia e Biotecnologie Mediche
e Forensi, Università degli Studi di Palermo, Palermo, Italy

Table 1 Classification of urticaria subtypes presenting with wheals and angioedema

Types	Subtypes	Definition
Spontaneous urticaria	Acute	Wheals with/without angioedema <6 weeks
	Chronic	Wheals with/without angioedema >6 weeks
Physical urticaria	Delayed pressure urticaria	Eliciting factor: vertical pressure
	Dermographic urticaria	Eliciting factor: mechanical shearing forces
	Solar urticaria	Eliciting factor: UV and/or visible light
	Heat urticaria	Eliciting factor: localized heat
	Cold urticaria	Eliciting factor: cold objects
	Vibratory urticaria	Eliciting factor: vibratory forces
	Other urticaria types	
Other urticaria types	Cholinergic urticaria	Increase of body core temperature
	Aquagenic urticaria	Eliciting factor: water
	Exercise induced urticaria	Eliciting factor: physical exercise
	Contact urticaria	Eliciting factor: urticariogenic substance

of the illness is acute, episodic or chronic, and irrespective of the aetiology, whether autoimmune, allergic, pseudoallergic, infection-related or spontaneous [1]. The challenge for the clinician is to find a cause to understand the clinical pattern if possible and to use this information to treat what is treatable, avoid the avoidable and provide symptomatic relief with antihistamines and second line pharmacological therapies, including antileukotrienes, corticosteroids and epinephrine when appropriate.

Evidence for autoimmunity

There is a wide portfolio of clinical and laboratory evidence for at least 30 % of patients with chronic spontaneous urticaria having an autoimmune aetiology [5–9]. It is possible that with better tests and clearer definition of what is meant by autoimmune urticaria, nearly all cases that would previously have been designated ‘spontaneous’ may be regarded as having an endogenous immunological cause for their urticaria, perhaps under genetic control. The nature of local events in skin leading to the release or synthesis of vasoactive mediators may only be discovered by real-time study of the cellular and molecular events leading to wheal formation. Detailed knowledge of this sort may well reveal heterogeneous biochemical and immunological disturbances leading to urticaria via a final common pathway rather than a single and identifiable abnormality that can be held up as the culprit for every case.

The epidemiology of urticaria

Urticaria is a common problem that appears to affect any age, all races and both sexes, although about two thirds of patients with chronic spontaneous urticaria are women, with a peak incidence in the fourth decade, consistent with the epidemiology of other autoimmune conditions, including

systemic lupus erythematosus and rheumatoid arthritis [2]. Although urticaria appears to be associated with atopy overall, there is no association between the ordinary presentation of chronic urticaria and atopic disorders. Large-scale epidemiological studies are lacking [10].

Genetic associations with urticaria

An association has been found between HLA DRB1*04 (encoding DR4) and its associated allele DQB1*0302 (encoding DQ8) in patients with chronic spontaneous urticaria compared with a healthy control population. The association was particularly strong for patients with in vivo and in vitro evidence of histamine-releasing activity, but was also present without [11, 12]. More autoimmune diseases have been associated with the HLA region than with any other genetic region. HLA-DR4 is also associated with rheumatoid arthritis and several autoimmune blistering diseases. More recently, significant associations have been found between polymorphisms of the TGF- β 1 gene promoter in chronic spontaneous urticaria and the high affinity IgE receptor alpha subunit (Fc ϵ RI α) promoter and aspirin-sensitive chronic urticaria [13, 14]. Another working hypothesis is that polymorphisms of cyclo-oxygenases and 5-lipo-oxygenase-activating protein may be involved in the pathways leading to chronic spontaneous urticaria [15].

Association between chronic urticaria and organ-specific autoimmunity

There have been several studies confirming the initial observation of an association between thyroid autoimmunity and chronic spontaneous urticaria [16]. Antithyroid antibodies were significantly more frequent in chronic urticaria patients with functional autoantibodies on the basophil histamine-release assay and with a positive autologous serum skin test ASST [17, 18].

Chronic urticaria has also been associated with coeliac disease in children and with a history of other autoimmune disorders including vitiligo, insulin-dependent diabetes, rheumatoid arthritis and pernicious anaemia [19, 20]. It is notable that no association has been found between markers of non-organ-specific autoimmunity, including antinuclear, smooth muscle and mitochondrial antibodies in any study to date.

The autologous serum skin test

The first demonstration of something in the sera of patients with chronic spontaneous urticaria in 1986 that was able to induce a wheal and flare response on intradermal re-injection initiated a chain of events that culminated in the evaluation of a novel autoantibody directed against the FcεRIα subunit 7 years later although this was not at all clear at the time [21, 22]. The initial hypothesis that the active factor might be an immune complex was not confirmed on skin testing of fractions separated by ultrafiltration and column chromatography, but at least low molecular weight mediators, such as histamine and bradykinin, were excluded. The test became known as the autologous serum skin test (ASST). A positive response (ASST+) was present in around 50–60 % of chronic spontaneous urticaria patients recruited from secondary and tertiary referral clinics and became negative after sustained clinical remission and therefore appeared to be relevant to the disease [21]. Biopsy showed an early

neutrophilic and eosinophilic cellular response with deposition of eosinophilic major basic protein and a light but progressive lymphocytic infiltration that was still present after 48 h [23, 24]. However, it was the subsequent recognition that sera and purified IgG of about 50 % of patients with ASST+ chronic spontaneous urticaria also released substantial amounts of histamine from healthy donor basophils in vitro that endowed the ASST with a reputation that it was a simple clinical screening test for functional autoantibodies [25]. This view has been challenged on several grounds: skin reactivity persisted after depletion of IgG and has also been demonstrated in low molecular weight fractions of chronic spontaneous urticaria sera [26, 27]. Demonstration of anti-FcεRIα autoantibodies by sensitive ELISA immunoassays in chronic spontaneous urticaria sera did not correspond well to ASST reactivity [26] or in vitro histamine-releasing activity on basophils [28]. The strengths and weakness of the ASST in the assessment of autoimmune urticaria are summarized in Table 2.

Therefore, the ASST has been interpreted simplistically as a test of autoimmune urticaria. Unfortunately, the evidence for the ASST is not completely convincing. The presence of an ASST positive is related with the presence in the serum of the patients with urticaria. The factors acting directly on the microvasculature of skin or indirectly through the release of mediators derive from cutaneous mast cells. The autoreactivity does not define autoimmune urticaria, but may be an indication of mast cell activating

Table 2 Strengths and weaknesses of tests for autoimmune urticaria

	Strengths	Weaknesses
ASST	Simple, cheap clinical test In widespread use Assesses autoreactivity Response relates to the cutaneous mast cell that is the primary effector cell of urticaria	Moderate sensitivity and specificity for in vitro HR Not specific for chronic ordinary urticaria Not a perfect model for spontaneous wheals Poor predictive value for response to immunotherapies
BHRA	Fairly simple assay Serum histamine-releasing activity is stable for freezing and transport Test is now commercially available Currently the best test of functional autoantibodies	Requires donor blood for basophil preparation Response differs between basophil donors Serum rather than IgG used as the stimulus Basophils are not mast cells
MCHRA	The relevant cell in skin used as substrate Results correlate with the BHRA Positive releasers only found in patients with a positive ASST	Mast cell isolated from newborn foreskin Impractical as a routine assay Relatively small numbers of patients studied to date
Immunoassays	Western blot is a routine laboratory assay Identifies specific target proteins and immunoglobulin classes precisely	Can not distinguish between functional and non-functional autoantibodies Anti-FcεRIα and anti-IgE detectable by ELISA in normals as well as chronic ordinary urticaria

ASST autologous serum skin test, BHRA basophil histamine-release assay, MCHRA mast cell histamine-release assay, Immunoassays Western blot and enzyme-linked immunosorbent assay (ELISA)

autoantibodies in the serum of patients with urticaria and ASST positive. Consequently, the function of these autoantibodies need to be confirmed by basophil histamine-release assay, and their specificity confirmed by Western blot or ELISA.

Laboratory evidence

Basophil histamine-release assay

It rapidly became clear that some chronic spontaneous urticaria sera had potent histamine-releasing properties, with a similar time course to the well-known immunological stimulus, anti-IgE. Initial characterization of these sera on the basophils of an atopic donor showed that some had the properties of anti-IgE, but others did not stimulate IgE sensitized basophils [24]. Further work on this subgroup of sera showed that they could stimulate basophils from a non-atopic donor, and atopic basophils from which the IgE had been artificially 'stripped' giving birth to the concept that a novel autoantibody was present, which could initiate degranulation by direct stimulation of Fc ϵ RI. The concept was confirmed by elegant experiments involving the neutralization of anti-Fc ϵ RI by the soluble fragment of the Fc ϵ RI α subunit prior to incubation of the sera, or IgG derived from them, with basophils from a healthy non-atopic donor. The basophil histamine-release assay is now commercially available (RefLab, Denmark). However, there are a number of weaknesses and valid criticisms of the basophil histamine-release assay (BHRA) as a definitive test for functional autoantibodies (Table 2). Firstly, basophils are not mast cells. There are also differences in phenotype and behaviour between mast cells derived from the skin and other tissues. Some authorities believe that basophils have greater similarity to eosinophils than tissue mast cells. Secondly, the BHRA is performed routinely with whole sera rather than purified IgG or its subclasses. Circulating cytokines and complement influence the releasability of basophils. Basophil histamine-release is complement dependent in a proportion of patients, and interleukin 3 increases the amount of histamine-release, but not the threshold for release. It is routinely used to 'prime' basophils for the BHRA in some laboratories. In other words, the functionality of the assay is not exclusively the result of anti-Fc ϵ RI autoantibodies binding the Fc ϵ RI. There may well be other essential histamine-releasing co-factors in the blood of chronic urticaria patients that are not present or relevant in patients without urticaria. Thirdly, it is well recognized that basophils from some donors do not release with immunological stimuli including anti-IgE and anti-Fc ϵ RI. It used to be thought that this was due to a genetic deficiency in the tyrosine kinase Syk that is an

essential proximal signalling molecule involved in degranulation. Recent studies indicate that Syk deficiency may be found in chronic spontaneous urticaria and that anti-IgE signalling pathways can be maintained without it. Endogenous regulation of signalling is also under the control of a more downstream negative regulator, src homology 2 domain-containing inositol 5' phosphatase (SHIP), overexpression of which downregulates basophil releasability. Selection of basophil donors for the BHRA may therefore influence the results. It has been shown that increasing the number of donors for the BHRA increased the number of positive results in ASST+ chronic spontaneous urticaria [25].

Mast cell histamine-release assays

Because mast cells rather than basophils are the primary effector cell of urticaria, it was important to demonstrate that they could also be activated by chronic spontaneous urticaria sera in vitro. An excellent correlation was observed between basophil and mast cell release by Ferrer et al. [28]. The same group went on to demonstrate the complement dependence of histamine-release by chronic urticaria sera on mast cells isolated from newborn foreskins [29]. Mast cell histamine-release assays would therefore appear to be the ideal assay for histamine-releasing autoantibodies in chronic urticaria in view of the correlation between mast cell and basophil histamine-release and the restriction of positive results to patients with a positive ASST, but the number of patients studied to date has been small, and isolation of mast cells from newborn foreskin for the routine assay would be impractical.

Immunoassays (Western blot and ELISA)

Although the functional assays described above provide good evidence for the presence of autoantibodies with specificity for IgE and Fc ϵ RI; the preparation of purified IgG for testing is time-consuming and not suited to a routine clinical assay. A much better assay for autoantibodies with a particular specificity and isotype would be an immunoassay. Fiebiger et al. were the first to explore this and found that IgG autoreactivity against immobilized soluble Fc ϵ RI α on Western blot was present in 37 % of chronic urticaria sera but not in atopic dermatitis sera, whereas anti-IgE was present in sera from chronic urticaria, atopic dermatitis and healthy controls [8].

Other tests of autoimmune urticaria

Basophil numbers, blood total cellular histamine, basophil releasability and expression of activation markers have been shown to relate to the presence functional

autoantibodies. Although they have not been used for diagnostic purposes individually, they may prove to be useful biomarkers for patients with autoimmune urticaria when taken in conjunction with other features of it. Basopenia in chronic urticaria was first noted in 1961 and subsequently confirmed in many studies. Almost complete absence of stainable peripheral blood basophils was noted by flow cytometry in patients with a positive BHRA [8, 30]. Detection of activation markers on basophils has been a subject of interest in the last 3 years and holds promise as a potential marker of autoimmune urticaria in the future. CD63 (glycoprotein 53) is upregulated on activation of basophils. It was induced in healthy donor basophils by incubation with chronic urticaria sera. The mean percentage expression of CD63 was significantly higher with sera from ASST+ than ASST− patients. Patients with a positive basophil activation test result also had significantly more severe urticaria [31]. A significant correlation was found between CD63 expression and histamine-release from healthy donor basophils [32]. A significantly higher induction of CD63 expression was found in healthy donor basophils incubated with sera from ASST+ than ASST− patients [33]. When comparing expression of activation markers on basophils from chronic urticaria patients, only CD63 was upregulated more than healthy controls in a small number of patients, whereas there was no change in the expression of CD203c [33].

Other immunological abnormalities in chronic urticaria

Other autoantibodies of potential relevance to autoimmune urticaria have been reported in chronic urticaria including anti-endothelial cell antibodies and anti-FcεRII (low affinity IgE receptor) antibodies which result in degranulation of eosinophils with release of major basic protein causing secondary histamine-release from peripheral blood basophils [34, 35]. Mediator release from human foreskin mast cells resulted in increased expression of intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E-selectin, which could be partly inhibited by treatment with antitumour necrosis-factor [36, 37]. Upregulation of bcl-2 expression (an apoptosis inhibitor) and increased expression of CD40L on activated peripheral blood T-cells were consistent with an observed proliferation of B cells [38].

Conclusion

Currently, the major ideas concerning the cause, pathogenesis or both of chronic spontaneous urticaria are based on observations suggesting that it has an autoimmune cause in 40–45 % of patients. There is the association with

antithyroid antibodies, which appear to be a marker of autoimmunity; the pathogenic antibodies are IgG anti-IgE receptor or IgG anti-IgE. The IgG antibodies activate the classical complement cascade, and purification of IgG subclasses demonstrated histamine-releasing activity predominantly within subclasses 1 and 3. If correct, future studies will elucidate the mechanistic details further, which might lead to new approaches regarding therapy.

In conclusion, patients with chronic spontaneous urticaria can be divided into two groups: with autoantibodies and without autoantibodies. The autoantibodies found in the serum of patients with chronic spontaneous urticaria are IgG antibody to the alpha subunit of the IgE receptor (35–40 %) usually reactive with unoccupied IgE receptors, or IgG antibody to IgE (5–10 %). Often in patients with autoantibodies are also associated antithyroid antibodies (27 %), and other autoimmune conditions such as vitiligo, rheumatoid arthritis and pernicious anaemia. The patients with demonstrable histamine-releasing autoantibodies have a very strong association with HLA-DR4 and its associated allele HLA-DQ8.

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References

1. Zuberbier T, Asero R, Bindslev-Jensen C, Walter Canonica G, Church MK, Giménez-Arnau A, Grattan CE, Kapp A, Merk HF, Rogala B, Saini S, Sánchez-Borges M, Schmid-Grendelmeier P, Schünemann H, Staubach P, Vena GA, Wedi B, Maurer M (2009) Dermatology Section of the European Academy of Allergology and Clinical Immunology; Global Allergy and Asthma European Network; European Dermatology Forum; World Allergy Organization. AACI/GA(2)LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria. *Allergy* 64:1417–1426
2. Greaves MW, Tan KT (2007) Chronic urticaria: recent advances. *Clin Rev Allergy Immunol* 33:134–143
3. Di Lorenzo G, Pacor ML, Mansueto P, Martinelli N, Esposito-Pellitteri M, Lo Bianco C, Ditta V, Leto-Barone MS, Napoli N, Di Fede G, Rini G, Corrocher R (2005) Food-additive-induced urticaria: a survey of 838 patients with recurrent chronic idiopathic urticaria. *Int Arch Allergy Immunol* 138:235–242
4. Tüzün Y, Keskin S, Kote E (2010) The role of *Helicobacter pylori* infection in skin diseases: facts and controversies. *Clin Dermatol* 28:478–482
5. Hide M, Francis D, Grattan C, Hakimi J, Kochan J, Greaves M (1993) Autoantibodies against the high-affinity IgE receptor as a cause of histamine release in chronic urticaria. *N Engl J Med* 328:1599–1604
6. Fiebiger E, Maurer D, Holub H et al (1995) Serum IgG autoantibodies directed against the alpha chain of Fc epsilon RI: a selective marker and pathogenetic factor for a distinct subset of chronic urticaria patients? *J Clin Invest* 96:2606–2612

7. Niimi N, Francis D, Kermani F et al (1996) Dermal mast cell activation by autoantibodies against the high affinity IgE receptor in chronic urticaria. *J Invest Dermatol* 106:1001–1006
8. Tong L, Balakrishnan G, Kochan J, Kinet J, Kaplan A (1997) Assessment of autoimmunity in patients with chronic urticaria. *J Allergy Clin Immunol* 99:461–465
9. Kikuchi Y, Kaplan A (2001) Mechanisms of autoimmune activation of basophils in chronic urticaria. *J Allergy Clin Immunol* 107:1056–1062
10. Kaplan AP (2009) What the first 10,000 patients with chronic urticaria have taught me: a personal journey. *J Allergy Clin Immunol* 123:713–717
11. O'Donnell BF, O'Neill CM, Francis DM, Niimi N, Barr RM, Barlow RJ et al (1999) Human leucocyte antigen class II associations in chronic idiopathic urticaria. *Br J Dermatol* 140:853–858
12. Pacor ML, Di Lorenzo G, Mansueto P, Martinelli N, Esposito-Pellitteri M, Pradella P, Uxa L, Di Fede G, Rini G, Corrocher R (2006) Relationship between human leucocyte antigen class I and class II and chronic idiopathic urticaria associated with aspirin and/or NSAIDs hypersensitivity. *Mediators Inflamm* 1:1–5
13. Hosseini-Farahabadi S, Tavakkol-Afshari J, Ganjali R, Rafatpanah H, Ghaffari J, Farid-Hosseini R (2006) Association between the polymorphism of TGF- β 1 gene promoter (–509C > T) and idiopathic chronic urticaria. *Iran J Allergy Asthma Immunol* 5:109–113
14. Bae J-S, Kim S-H, Ye Y-M, Yoon HJ, Suh C-H, Nahm D-H et al (2007) Significant association of Fc ϵ RI α promoter polymorphisms with aspirin-intolerant chronic urticaria. *J Allergy Clin Immunol* 119:1280–1281
15. Di Lorenzo G, Pacor ML, Candore G, Listi F, Ditta V, Leto-Barone MS, D'Alcamo A, Martinelli N, Corrocher R, Caruso C (2011) Polymorphisms of cyclo-oxygenases and 5-lipo-oxygenase-activating protein are associated with chronic spontaneous urticaria and urinary leukotriene E4. *Eur J Dermatol* 21:47–52
16. Leznoff A, Sussman GL (1989) Syndrome of idiopathic chronic urticaria and angioedema with thyroid autoimmunity: a study in 90 patients. *J Allergy Clin Immunol* 84:66–71
17. Kikuchi Y, Fann T, Kaplan AP (2003) Antithyroid antibodies in chronic urticaria and angioedema. *J Allergy Clin Immunol* 112:218
18. O'Donnell BF, Francis DM, Swana GT, Seed PT, Kobza Black A, Greaves MW (2005) Thyroid autoimmunity in chronic urticaria. *Br J Dermatol* 153:331–335
19. Caminiti L, Passalacqua G, Magazzu G, Comisi F, Vita D, Barberio G et al (2005) Chronic urticaria and associated coeliac disease in children: a case-control study. *Pediatr Allergy Immunol* 16:428–432
20. Sabroe RA, Seed PT, Francis DM, Barr RM, Kobza Black A, Greaves MW (1999) 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* 40:443–450
21. Grattan CEH, Wallington TB, Warin RP, Kennedy CTC, Bradfield JW (1986) A serological mediator in chronic idiopathic urticaria—a clinical, immunological and histological evaluation. *Br J Dermatol* 114:583–590
22. Hide M, Francis DM, Grattan CEH, Hakimi J, Kochan JP, Greaves MW (1993) Autoantibodies against the high-affinity IgE receptor as a cause of histamine release in chronic urticaria. *N Eng J Med* 328:1599–1604
23. Grattan CEH, Boon AP, Eady RAJ, Winkelmann RK (1990) The pathology of the autologous serum skin test response in chronic urticaria resembles IgE-mediated late-phase reactions. *Int Arch Allergy Appl Immunol* 93:198–204
24. Grattan CEH, Francis DM, Hide M, Greaves MW (1991) Detection of histamine releasing autoantibodies with functional properties of anti-IgE in chronic urticaria. *Clin Exp Allergy* 21:695–704
25. Sabroe RA, Grattan CEH, Francis DM, Barr RM, Kobza Black A, Greaves MW (1999) The autologous serum skin test: a screening test for autoantibodies in chronic idiopathic urticaria. *Br J Dermatol* 140:446–452
26. Fagiolo U, Kricek F, Ruf C, Peserico A, Amadori A, Cancian M (2000) Effects of complement inactivation and IgG depletion on skin reactivity to autologous serum in chronic idiopathic urticaria. *J Allergy Clin Immunol* 106:567–572
27. Grattan CEH, Hamon CGB, Cowan MA, Leeming RJ (1988) Preliminary identification of a low molecular weight serological mediator in chronic idiopathic urticaria. *Br J Dermatol* 119:179–184
28. Ferrer M, Kinet J-P, Kaplan AP (1998) Comparative studies of functional and binding assays for IgG anti-Fc ϵ RI α (α -subunit) in chronic urticaria. *J Allergy Clin Immunol* 101:672–676
29. Sabroe RA, Francis DM, Barr RM, Kobza Black A, Greaves MW (1998) Anti-Fc ϵ RI autoantibodies and basophil histamine releasability in chronic idiopathic urticaria. *J Allergy Clin Immunol* 102:651–658
30. De Swert A, Van den Keybus C, Kasran A, Cadot P, Neyens K, Coorevits L et al (2005) Detection of basophil-activating IgG autoantibodies in chronic idiopathic urticaria by induction of CD63. *J Allergy Clin Immunol* 116:662–667
31. Szegedi A, Irinyi M, Gal M, Hunyadi J, Danko K, Kiss E et al (2006) Significant correlation between the CD63 assay and the histamine release assay in chronic urticaria. *Br J Dermatol* 155:67–75
32. Vasagar K, Vonakis BM, Gober LM, Viksman A, Gibbons SP, Saini SS (2006) Evidence of in vivo basophil activation in chronic idiopathic urticaria. *Clin Exp Allergy* 36:770–776
33. Pucetti A, Bason C, Simeoni S, Millo E, Tinazzi E, Beri R et al (2005) In chronic idiopathic urticaria autoantibodies against the Fc ϵ RII/CD23 induce histamine release via eosinophil activation. *Clin Exp Allergy* 35:1599–1607
34. Piconi S, Trabattini D, Lemoli E, Fusi ML, Villa ML, Milazzo F et al (2002) Immune profiles of patients with chronic idiopathic urticaria. *Int Arch Allergy Immunol* 128:59–66
35. Tan EM (1982) The 1982 revised criteria for the classification of systemic LE (SLE). *Arthritis Rheum* 25:1271–1277
36. Grattan CEH (2004) Autoimmune urticaria. *Immunol Allergy Clin N Am* 24:163–181
37. Grattan CEH, D'Cruz DP, Francis DM, Whiston C, Hughes GRV, Greaves MW (1995) Antiendothelial cell antibodies in chronic urticaria. *Clin Exp Rheumatol* 13:272–273
38. Platzer MH, Grattan CEH, Poulsen LK, Skov PS (2005) Validation of basophil histamine release against the autologous serum skin test and outcome of serum-induced basophil histamine release studies in a large population of chronic urticaria patients. *Allergy* 60:1152–1156