

The autoimmune nature of chronic urticaria

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ABSTRACT

The association between chronic urticaria (CU) and autoimmune disease has been recognized for some time, especially with autoimmune thyroid disease. More recently, functional IgG autoantibodies against FcepsilonRIalpha and less commonly against IgE have been reported in a subset of patients with CU. These patients have been described as having more severe and difficult-to-control urticaria. The autologous serum skin test has been proposed as a surrogate test to define presence of these autoantibodies, although it identifies presence of histamine releasing factor, not necessarily antibody. Basophil histamine release and basophil activation assays using flow cytometry to measure CD63 and, more recently, CD203c expression have been used to identify patients with autoimmune urticaria. New research suggests that in some patients with CU, the activation of the extrinsic coagulation pathway with thrombin generation might play an important role in their CU.

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Key words: Anti-FcepsilonRIalpha, antithyroid antibodies, autoimmune thyroid disease, autoimmune urticaria, autologous serum skin test, CD63, CD203c, chronic urticaria, histamine release, urticaria

Guidelines for evaluation and management of urticaria in children and adults were recently published.¹ Under clinical classification of the urticarias, chronic urticaria (CU) is a subset of ordinary urticaria and is defined as ≥ 6 weeks of continuous urticarial activity (Table 1). In terms of etiology, autoimmune urticaria is a subset of immunologic urticarias (Table 2). This review will focus on autoimmune aspects of this vexing disease and new insights into pathophysiology, previously reviewed in this Journal.²

CHRONIC URTICARIA (CU) AND AUTOIMMUNE DISEASES

In 1983, Leznoff *et al.*³ first reported on the association between CU and autoimmune thyroid disease. Autoimmune thyroid disease was documented in 17 of 140 (12.1%) consecutive patients with CU. This author subsequently described 90 of 624 (14.4%) patients with

CU and angioedema with thyroid autoimmunity.⁴ This study included children as young as 8 years of age and a female/male ratio of 7:1 was observed. The only laboratory abnormalities involved thyroid function and antithyroid antibodies. In this cohort, a small subset of patients responded to treatment with thyroid hormone with resolution of hives. Recently, Monge *et al.*⁵ reported that 3–6% of the population has antithyroid antibodies, making thyroid autoimmunity the most common of the organ-specific autoimmune processes. An increased frequency of thyroid disease occurred in both children and adults with CU. In their study, CU was associated with autoimmune thyroid disease irrespective of the presence of euthyroid state, hyperthyroidism, hypothyroidism, or presence of antithyroid antibodies.⁵ These authors hypothesized that cellular immunity initiated in the thyroid gland could trigger development of skin lesions. Small groups of V β 8-restricted T lymphocytes have been found in skin biopsy specimens of patients with CU and also in thyroid glands of patients with Hashimoto's thyroiditis and could participate in the pathogenesis of CU, although this remains unproven.

A prospective study of 99 patients found the frequency of antithyroglobulin and antithyroid peroxidase antibodies in CU patients to be 26.7% compared with 3.3% in healthy subjects ($p < 0.01$).⁶ In another study, antithyroglobulin antibodies were present in 22.2% and antithyroid peroxidase in 26.8% of a series of 56 patients with CU, confirming the frequency of thyroid antibodies in CU.⁷ Rumbyrt *et al.*⁸ suggested

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Table 1. Clinical classification of urticaria

Ordinary urticaria
Acute (up to 6 weeks of continuous activity)
Chronic (6 weeks or more of continuous activity)
Episodic (acute intermittent or recurrent activity)
Physical urticarias (reproducibly induced by the same physical stimulus)
Mechanical
Delayed pressure urticaria
Symptomatic dermatographism
Vibratory angioedema
Thermal
Cholinergic urticaria
Cold contact urticaria
Localized heat urticaria
Other
Aquagenic urticaria
Solar urticaria
Exercise-induced anaphylaxis
Angioedema without weals
Idiopathic
Drug-induced
C1 esterase inhibitor deficiency
Contact urticaria (contact with allergens or chemicals)
Urticarial vasculitis (defined by vasculitis on skin biopsy)
Autoinflammatory syndromes
Hereditary
Cryopyrin-associated periodic syndromes (CIAS1 mutations)
Acquired
Schnitzler syndrome

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that a trial with levothyroxine may be warranted after failure of conventional therapy in CU patients with antithyroid antibodies who were euthyroid. In their patients with CU who had detectable antithyroid antibodies, all responded to the thyroid hormone with improvement of their urticaria. Limited studies further suggest that treatment with levothyroxine may be beneficial in CU patients even when antithyroid antibodies are not detectable with the goal of lowering thyroid-stimulating hormone to 0.50–2.0 mU/L, as >95% of normal individuals have a thyroid-stimulating hormone level <2.50 mU/L.⁵ Practical aspects of this therapeutic approach were extensively reviewed by Schocket in this Journal.²

Autoimmune diseases in association with CU have been reported in children, though less frequently than in adults. In addition to thyroid autoimmunity, juvenile rheumatoid arthritis, systemic lupus erythematosus, insulin-dependent diabetes mellitus, and celiac

Table 2. Etiology of urticaria

Idiopathic
Immunological
Autoimmune (autoantibodies against FcεRI or IgE)
Allergic (IgE-mediated type I hypersensitivity reactions)
Immune complex (urticarial vasculitis)
Complement-dependent (C1 esterase inhibitor deficiency)
Nonimmunological
Direct mast cell-releasing agents (<i>e.g.</i> , opiates)
Aspirin, nonsteroidal anti-inflammatories and dietary pseudoallergens
Angiotensin-converting enzyme inhibitors

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disease have all been reported in association with CU.^{9,10} Of note, urticaria angioedema can precede, occur concomitantly with or appear after the diagnosis of autoimmune disease. Thus, some authors suggest periodically repeating screening tests for autoimmune diseases in children whose CU persists.

AUTOIMMUNE URTICARIA

A subset of patients with CU has complement-activating (C5a), histamine-releasing IgG autoantibodies that degranulate mast cells and basophils by binding to the α -chain of the high-affinity IgE receptor.¹¹ The chronology of events that led to our current understanding is briefly summarized. In 1986, a serological factor was first reported in some patients with CU, which caused wheals when injected intradermally.¹² In 1988, anti-IgE autoantibodies were described in patients with urticaria, some of which appeared to be functional and a role for autoantibodies in urticaria was first proposed.¹³ In 1991, histamine-releasing autoantibodies with functional properties of anti-IgE were found in patients with CU.¹⁴ In 1993, IgG class antibodies directed against the α -chain of the high-affinity IgE receptor (FcεRI) were identified.¹⁵ Subsequently, in 1998, a functional role for these autoantibodies was shown by *in vitro* release of histamine from basophils and dermal mast cells.¹⁶ In 1999, patients with CU with histamine-releasing autoantibodies were shown to have more severe urticaria compared with patients with CU without such autoantibodies.¹⁷ Finally, in 2001 and 2002, histamine release from basophils activated by IgG autoantibodies directed against the α -subunit of FcεRI was shown to be augmented by serum complement and that complement activation liberated C5a.^{18,19} C5a participates in mast cell activation in patients with CU who have functional anti-FcεRI α autoantibodies (Fig. 1). Other patients with

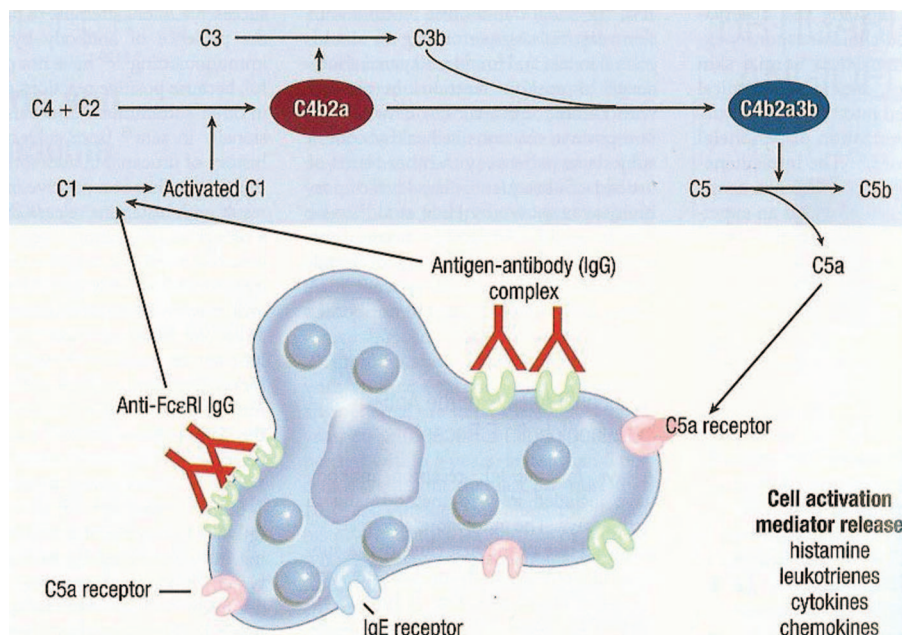


Figure 1. Activation of cutaneous mast cells by antireceptor antibody followed by activation of complement with generation of C5a and augmentation of mast cell mediator release. (Reproduced with permission from Ref. 46)

CU have been shown to have anti-IgE antibodies or nonantibody serum histamine-releasing factor.¹¹ The prevalence of autoantibodies in patients with CU in one study was found to be histamine-releasing anti-FcεRI antibodies, 26%; nonhistamine-releasing anti-FcεRI antibodies, 15%; anti-IgE antibodies, 9%; mast cell-specific nonantibody histamine-releasing factor, 9%; and no identifiable factor, 41% (Fig. 2).²⁰

Sabroe *et al.*²¹ recently reviewed the possible explanations for the latter findings. In the subset of CU patients and no identifiable factor, the question remains if antibodies may be present, but tests lack adequate sensitivity to detect them. However, increasing the sensitivity of the *in vitro* basophil histamine release assay using IL-3 has not been shown to increase the proportion of positive sera.²² Substituting human dermal mast cells for basophils has been shown to increase the number of positive sera in some studies²³ but not in others.²⁰ Other nonantibody factors were also considered. Mast cell-specific histamine-releasing factor of >30 kD, which is not an immunoglobulin, has been partially characterized.²⁴ A distinct histamine-releasing factor; a cytokine produced by peripheral blood mononuclear cells, which enhances basophil histamine release and modulates secretion of cytokines from basophils; eosinophils; and T cells has been described also.^{25,26} Finally, a cellular or subcellular, rather than humoral factor could be involved as aberrant regulation of the p21 Ras pathway in peripheral blood mononuclear cells of patients with CU has been reported.²⁷

Nonfunctional anti-FcεRI autoantibodies have been detected in serum of patients with autoimmune dis-

eases such as dermatomyositis and pemphigus and in a few patients with physical urticarias, as well as in patients with CU.¹⁶ These nonhistamine-releasing autoantibodies have been shown to be predominantly IgG2 and IgG4 subclass, which do not activate complement. In contrast, histamine-releasing autoantibodies are predominantly IgG1 and IgG3 subtypes that can activate complement.²⁸

Autoimmune urticaria has not been studied as extensively in children. Initially, Greaves described an 11-year-old boy with steroid-dependent CU with anti-FcεRIα IgG autoantibodies.²⁹ Subsequently, Brunetti *et*

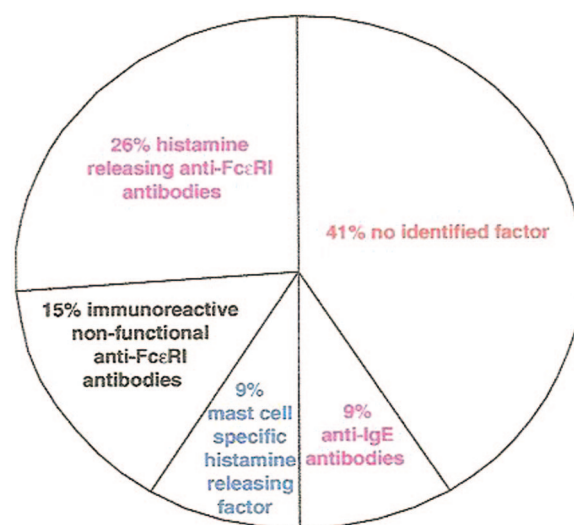


Figure 2. Prevalence of autoantibodies in patients with chronic urticaria. (Reproduced with permission from Ref. 21).

*al.*³⁰ reported a prevalence of 31% in children with CU. More recently, in a study comparing children with CU versus those with atopic dermatitis, anti-FcεRI autoantibodies were found in 37 of 78 children with CU (47%) versus 0 in 33 children with atopic dermatitis.³¹ In addition, non-IgG histamine-releasing factors were found in 10 of 78 children with CU (13%). Thus, the prevalence appears similar to that reported in adults.²⁰

In a recent study that compared clinical and laboratory features of patients with autoimmune urticaria versus chronic idiopathic urticaria and physical urticaria, urticaria scores were significantly elevated in the autoimmune urticaria group, as were individual parameters including pruritus, frequency, duration, and distribution of wheals.³² In addition, patients with autoimmune urticaria were more likely to require third-line treatment (cyclosporin). These results support previous studies in patients with autoimmune urticaria.³³

Screening tests for functional autoantibodies in CU includes *in vivo* evaluation with the autologous serum skin test (ASST).²¹ It is worth noting that the ASST does not prove the presence of antibodies, but rather shows histamine-releasing properties of the tested serum. The sensitivity and specificity of this intradermal test for autoantibody detection in patients with CU is reported to be 80% at best when compared with the *in vitro* basophil histamine release assay.²¹ In pediatric populations, studies have shown both a correlation between a positive ASST result and a histamine releasability (sensitivity, 78%; specificity, 85%),³⁰ as well as lack of any significant correlation between the ASST and presence of FcεRIα autoantibodies or histamine-releasing factors ($p = 0.46$).³¹ More recently, use of autologous plasma rather than serum resulted in a 95% rise in intradermal skin test response.³⁴ This suggests that clotting may deplete a plasma factor involved in the positive response.

In vitro tests include measuring histamine release from basophils or dermal mast cells. Basophils are both lactic acid stripped to remove IgE for detection of anti-FcεRI autoantibodies and IgE sensitized for detection of anti-IgE autoantibodies.²¹

In a study of 182 patients with CU, 90 patients had a positive ASST and of this group, 40 had positive histamine release *in vitro* and were defined as the autoimmune subgroup, while 50 had negative *in vitro* histamine release assays.³⁵ Of those with a negative ASST, all 92 also had negative histamine release assays. Recently, Kaplan *et al.*³⁶ studied differences in basophil histamine release and showed that patients with autoimmune urticaria had mean percentage HR of 59% versus 5.6% in chronic idiopathic urticaria and 0.47% in allergic subjects without urticaria.

New directions in diagnosis of autoimmune CU includes measuring basophil activation markers CD63 and CD203c assays using flow cytometry.³⁷

CD63 is a basophil and mast cell activation marker expressed as a result of fusion between intracytoplasmic granules and the plasma membrane.³⁸ Szegedi *et al.*³⁹ showed a direct linear correlation between CD63 expression and histamine release. CD63 expression has been shown to be significantly increased on basophils from patients with CU and positive ASST versus patients with CU with negative ASST, systemic lupus erythematosus, dermatomyositis, or controls.⁴⁰ Frezzolini *et al.*⁴¹ showed that CD63 expression could be increased in response to ASST + CU sera when the source of basophils were atopic versus nonatopic donors ($p < 0.001$). However, CD63 can also be expressed on monocytes and platelets. In contrast, CD203c (ectonucleotide pyrophosphatase/phosphodiesterase) ectoenzyme is expressed only on basophils, mast cells, and CD34⁺ progenitor cells in peripheral blood as a marker of cell activation.⁴² Evaluation of patients with well-characterized autoimmune CU shows significant up-regulation of basophil CD203c *in vitro*.⁴³ Recently, this research tool has become available for clinical evaluation of patients with CU (Immunodiagnostic Laboratory, National Jewish Medical and Research Center).

The question of whether CU with functional anti-FcεRIα or anti-IgE autoantibodies is a distinct autoimmune disease has been raised.²¹ The argument for autoimmune disease includes reproducibility of ASST through passive transfer of serum of affected patients into skin of healthy individuals, correlation of functional autoantibodies plasma levels with disease severity, disease remission after removal (plasmapheresis) or suppression (i.v. immunoglobulin) of autoantibodies, strong association of HLA subtypes DRB1*04 (DR4) and DQB1*0302 (DQ8) with the subset of patients with autoantibodies, and association of CU with autoimmune thyroid disease. The argument against is that to date there is no animal model of autoimmune urticaria. On balance, this suggests that functional autoantibodies in CU are pathogenic.

New Concepts in CU

Patients with CU frequently show signs of thrombin generation due to activation of the extrinsic pathway of coagulation and signs of fibrinolysis as shown by increased mean D-dimer plasma levels.³⁴ Thrombin is a serine protease that may play a key role in urticaria, being able to induce edema through an increase in vascular permeability, mast cell activation, and degranulation, and to induce the production of the anaphylotoxin C5a.⁴⁴ In patients with severe CU, median levels of D-dimer and plasma prothrombin fragment F(1 + 2) largely exceeded those found in patients with mild CU (D-dimer, $p =$

0.001; $F[1 + 2]$, $p = 0.003$) and in normal subjects (D-dimer, $p = 0.0001$; $F[1 + 2]$, $p = 0.0001$).⁴⁵ Thus, although some patients with CU may have anti-FcεRI autoantibodies, in other patients the activation of the extrinsic coagulation pathway with thrombin generation might play an important role in their CU.⁴⁴ Whether the two mechanisms coexist, acting synergistically or are somehow linked or sequential, remains to be established.

Take-Home Messages

Patients with CU should be screened for an associated autoimmune disease, especially autoimmune thyroid disease. It is worth remembering that patients may be euthyroid and have antithyroid antibodies. In addition, CU can be an autoimmune disease in a significant number of patients, most commonly with IgG autoantibodies against FcεRIα and less commonly against IgE, especially in those with more severe and difficult-to-control urticaria. The ASST has been proposed as a surrogate test to define presence of these autoantibodies, although it identifies presence of histamine-releasing factor, not necessarily antibody. Basophil histamine release and basophil activation assays using flow cytometry to measure CD63 and, more recently, CD203c expression can be used to identify patients with autoimmune urticaria. In some patients with CU, the activation of the extrinsic coagulation pathway with thrombin generation might play an important role in their CU and D-dimer and plasma prothrombin fragment $F(1 + 2)$ would be elevated.

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