

Autoimmune Urticaria

LEONARD C. ALTMAN, M.D.

ABSTRACT

Urticaria persisting for longer than 6 weeks is defined as chronic. Rarely is this the result of allergy to an external food or inhalant allergen, although patients and most health professionals still make this assumption. In contrast, it is now established that approximately 50% of cases are caused by autoimmune IgG antibodies to the IgE receptor or IgE on mast cells and basophils. Clinically, this is detected by the autologous serum skin test or a recently developed *in vitro* assay. Antihistamines often at high doses or in combination are first-line therapy, but recalcitrant cases often require immune modulator therapy such as cyclosporin or methotrexate.

INTRODUCTION

URTICARIA has been a vexing disorder to patients and physicians throughout the history of medicine. It is generally classified as acute and chronic, based on duration, with 6 weeks of persistence dividing the two categories. Acute urticaria, by definition, is temporary and self resolves. It may be due to an identifiable allergen or in some cases accompanies an infectious disease.

The truly difficult situation is the patient who presents with chronic urticaria in which case there is almost never an historically evident etiology.¹ This is not to say that patients lack historical explanations, but that they are rarely validated by close scrutiny or testing. Most often, patients look for a cause in their diet and will falsely conclude they have food allergies, although the correlation is generally weak to nonexistent. Others will blame clothing, washing products, cosmetics or inhalants. Rarely are any of these explanations correct, and even if patients are shown by skin or blood tests to have specific IgE antibodies to food or inhalant allergens, these are generally not the direct cause of the urticaria.

The medical profession also has been responsible for creating false explanations for chronic urticaria. Older studies reported correlations between chronic urticaria and food preservatives and dyes, occult food allergens, and chronic indolent infections.^{2,3} In general, none of this work has stood the test of time or rigorous research.

In contrast, the only true advance in this field in the past 2 decades was the observation that approximately 50% of chronic urticaria patients have an autoimmune disorder and a circulating autoantibody responsible for disease induction. Malmros, in 1946, was the first to show that serum from patients with chronic urticaria could induce an immediate wheal and flare when injected intradermally.⁴ In 1986, the first detailed study was published showing that a significant percentage of patients with chronic "idiopathic" urticaria had a factor in their serum which caused a typical urticarial lesion when injected in the skin.⁵ This

Department of Medicine and Environmental Health, University of Washington School of Medicine, Seattle, Washington.

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phenomenon did not occur in normal subjects, and the active factor in the serum was shown to be heat stable at 56°C. Extensive work since then has validated this finding and showed that the serum factor is an IgG autoantibody which, in most cases, is directed against the IgE receptor on cutaneous mast cells.⁶⁻⁸ The skin test procedure used in this original paper is still very useful today, and is termed the autologous serum skin test or ASST.

PATHOGENESIS

Histamine released from cutaneous mast cells is the principle mediator of urticaria. This chemical is responsible for the increased pruritis and vascular permeability which characterizes urticarial lesions. Many stimuli can provoke histamine release from mast cells (Fig. 1). One mechanism of histamine release is allergen interaction with specific IgE on mast cells. This is the well-understood mechanism of allergic disease and can explain some cases of acute urticaria. It is rarely, however, a cause of chronic urticaria. In contrast, studies have shown that sera from about 50% of patients with chronic urticaria contain IgG antibodies that are directed against either the IgE receptor or IgE itself on basophils and mast cells.⁹ The anti-receptor antibodies bind either the $\alpha 2$ subunit of the receptor and compete with IgE for binding, or to the $\alpha 1$ subunit, in which case they are noncompetitive (Fig. 2). Other studies have suggested that only the IgG1 and IgG3 subclasses are responsible for autoimmune urticaria, and that complement activation is involved. IgG₁ and IgG₃ are efficient in activating the complement cascade leading to C5a generation, and this peptide is a potent histamine releaser from mast cells.

DIAGNOSIS

The standard test for detecting autoimmune antibodies is the ASST or autologous serum skin test. This is performed by injecting 50 μ L of autologous serum into the volar aspect of the forearm of the patient

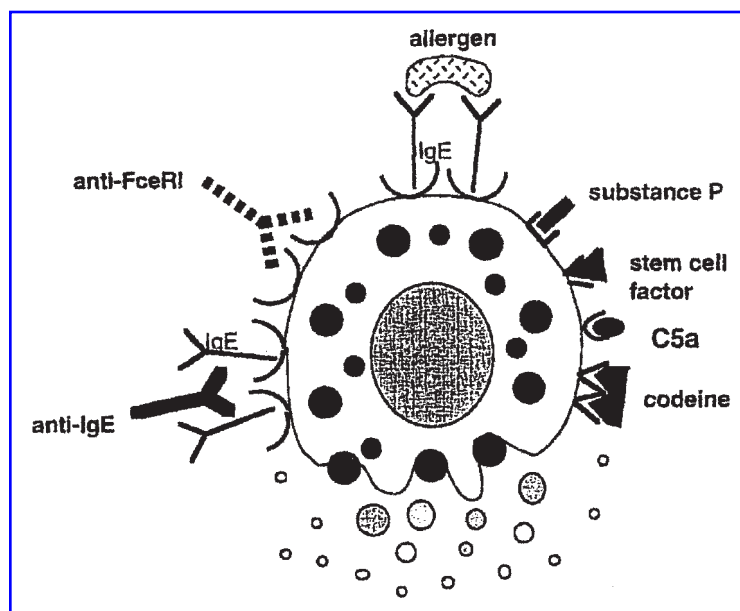


FIG. 1. A schematic diagram of a mast cell showing various mechanisms of degranulation. Allergen interaction with IgE is the conventional stimulus in allergic disease. Anti-Fc ϵ RI or anti-IgE antibodies are the etiologic mechanism of autoimmune urticaria. Codeine is an example of a nonimmunologic chemical mast cell degranulator. C5a is a histamine releaser derived from the complement cascade. Substance P is a polycationic peptide which stimulates mast cell degranulation by activation of G proteins. Stem cell factor is a potent cytokine important in mast cell differentiation, survival, migration, and degranulation.

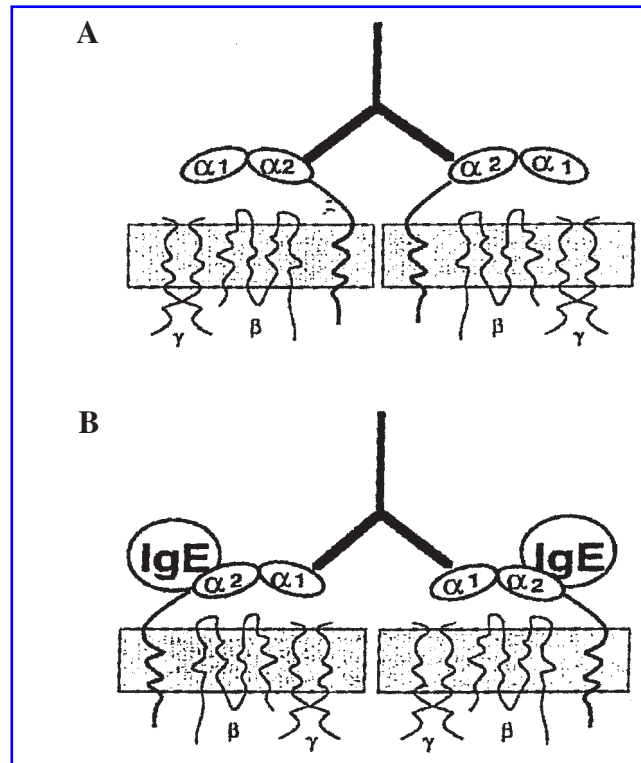


FIG. 2 (A). Autoantibodies that compete for the IgE binding site on the α_2 domain of Fc ϵ RI are competitive. **(B)** Autoantibodies that bind to the α_1 domain of Fc ϵ RI in the presence of IgE are noncompetitive.

with similar volumes of 0.9% saline as a negative control and 0.275 mg/mL histamine as a positive control. The wheal and flare size is recorded immediately and at 15 and 30 minutes. The definition of a positive response varies among reports from an increase of 1.5 mm wheal size, which, in the opinion of this author, is insufficient for accurate determination, to >50% than the histamine response. An increase in wheal size of at least 3 mm is probably a realistic end point. In research studies, ELISA and upregulation of basophil cell markers by flow cytometry have also been used for autoantibody detection. Only recently has a commercial *in vitro* test become available.¹⁰ Availability of this assay will allow dermatologists and primary care physicians who do not usually perform immediate hypersensitivity skin tests to make the diagnosis of autoimmune urticaria. This may be very useful to pediatricians, since skin testing is often too invasive in children. Furthermore, a recent study found that children with chronic urticaria have a similar incidence of autoimmunity as do adults.¹¹ Also helpful in diagnosis is the fact that other autoimmune disorders are common in patients with autoimmune urticaria or in their immediate relatives. Thyroid autoantibodies are more than twice as common in these patients as in the general population.¹² Other associated conditions are rheumatoid arthritis, insulin-dependent diabetes, systemic lupus, and pernicious anemia. Measurement of antithyroid and antinuclear antibodies can be helpful adjunctive tests in diagnosis. In general, clinical presentation does not differ significantly between patients who are ASST positive and negative. Both groups can have diffuse, episodic outbreaks of urticaria with and without angioedema, although those who are autoantibody positive generally have a more severe course.

TREATMENT

Initial treatment is the same for all patients with chronic urticaria, whether they have mast cell degranulating autoantibodies or not. First-line therapy is non or low sedating antihistamines. The first choice of

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this author is cetirizine starting at the approved dosage of 5 or 10 mg daily depending on patient age and advancing as needed to well above conventional levels, if tolerated. In adult patients up to 60 mg daily in divided doses can be used. Advancement from 10 to 60 mg can be achieved by most patients in about 7 days with tolerance to sedation being achieved by most. In children, appropriate dose reduction is needed. Fexofenadene, although somewhat less effective, has the advantage of being nonsedating even at high doses. It can be advanced as high as 360 mg twice daily in adults, or used as morning therapy combined with cetirizine at night, Hydroxyzine 10 to 75 mg or doxepin 10 to 30 mg at night can be effective, but both are sedating to most patients. Doxepin can prolong the QTc interval so physicians must take this into account and consider relevant drug interactions. Diphenhydramine is often effective but has a short half-life and is generally sedating or performance impairing at doses needed to achieve efficacy. Loratadine is generally ineffective as are leukotriene receptor antagonists and H₂ receptor antagonists.

Certain coincidental circumstances are also relevant. Alcohol ingestion often causes flares of urticaria because this agent is a vasodilator. Exacerbations may also be caused by nonsteroidal anti-inflammatory drugs, so both of these should be avoided. Urticaria often occurs when skin is tightly bound by clothing and patients should be advised to avoid this circumstance. Fatigue, stress, and intercurrent viral infections will often cause exacerbations.

In patients in whom antihistamines provide sufficient control most of the time, occasional flares may still occur. These can generally be controlled with a short burst of a corticosteroid, such as prednisone, 40 mg for 5 days and 20 mg for a similar duration. In children, a dose adjustment based on body weight is appropriate.

Unfortunately, some patients cannot be controlled with antihistamines, even at high doses and in combination. In allergy offices this is a daily occurrence. In these cases, a number of immunomodulatory drugs can be used. These include cyclosporine, hydroxychloroquine, methotrexate, sulfasalazine, dapsone, tacrolimus, and intravenous immunoglobulin. In the most severe cases, plasmapheresis has been employed.

Cyclosporine has been the most rigorously studied of these drugs and has been proven effective in patients with positive autologous skin tests in a double-blind placebo-controlled trial.¹³ It has, however, also been shown effective in patients with negative autologous skin tests.^{14,15} The doses used range from 2.5 to 5 mg/kg. Treatment is generally required for 3 to 4 months; however, pruritis is often reduced in days. Side effects include nephrotoxicity, hypertension, and elevation of serum lipids. These need to be monitored regularly while the cyclosporin is being taken. The drug is administered in addition to antihistamines. Cyclosporine should be withdrawn gradually, and in general, one-third of patients remain in remission after the drug is stopped. In another third, urticaria will return but can now be more effectively controlled with antihistamines alone. In the remaining one third, resumption of cyclosporin or another immune suppressant¹⁵ is needed.

Another choice is methotrexate. Published evidence for use of this drug is limited;¹⁶ however, it is the experience of this author that this drug is very effective. In uncontrolled clinical practice, weekly pulse therapy with this agent has been beneficial in producing control and/or complete remission in about 70% of patients. The drug is given weekly starting at 7.5 mg the first week and 15 mg each week thereafter. Folic acid 1 mg daily the other 6 days of the week is used to reduce hematologic and other side effects. The most common adverse reactions are nausea on the day of ingestion, elevation of liver enzymes, and hair loss. Approximately 90% of patients experience minimal to no side effects; however, complete blood counts and liver function tests should be checked monthly while the medication is being taken. Occasionally the dose needs to be increased to 20 or 25 mg weekly. Benefit is usually evident in 1 to 3 months. Once control is complete, antihistamines should be gradually reduced and stopped, and if the patient is symptom free without antihistamines, methotrexate can be reduced by 2.5 mg decrements weekly.

Hydroxychloroquine has also been used with benefit, but again, controlled studies are lacking.¹⁷ The usual adult dose is 200 mg twice daily. Serious side effects are infrequent, and include nausea, headache, anemia, and retinal damage. Patients who are G6PD deficient, which is more common among African-Americans, are at increased risk for anemia. Retinal damage is very rare but can cause color blindness or even vision loss. All patients taking hydroxychloroquine should have retinal examinations by an ophthalmologist every 6 months.

The other immune modulator drugs are rarely used and the reader is directed to the literature should they be needed.¹⁸⁻²¹

In summary, recognition of autoimmunity as a cause of nearly 50% of cases of chronic urticaria is the first substantial development in 2 decades. This finding has led to treatment of selected patients with immunomodulatory drugs, which has significantly reduced morbidity and often produced remission.

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Address reprint requests to:

Leonard C. Altman, M.D.

Medicine and Environmental Health Department

University of Washington School of Medicine

Seattle, WA 98105

E-mail: laltman@nwasthma.com

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