

Chronic urticaria: Pathophysiology and etiology, or the what and why

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ABSTRACT

Chronic urticaria (CU) is a relatively common but vexing disease. The pathophysiology is based on the cutaneous mast cell release of mediators, predominantly histamine. Release can be induced via specific immunoglobulin E (IgE), components of complement activation and nonspecifically by various compounds including endogenous peptides, endorphins, and enkephalins. In >30% of CU patients, autoimmune phenomena have been found, characterized by positive autologous serum skin test, antibodies to the α -subunit of the basophil IgE receptor, to IgE itself, and, perhaps, the most clinically relevant, thyroid autoimmunity. Studies suggest that the products of the activated immune system can lower the cutaneous mast cell release threshold, possibly allowing activation by endogenous compounds. The resulting release of mediators produces the clinical picture of recurrent hives. Although the goal of management of CU is the identification of a treatable cause, in most CU patients, especially adults, a cause is not frequently found. Identified causes include drugs, foods, infections, immune complex production leading to urticarial vasculitis, autoantibody production, and underlying autoimmune disease, particularly autoimmune thyroiditis. The treatment of the thyroiditis with suppressive doses of thyroid hormone often results in the remission of the CU. Given the marginally effective and sometimes dangerous medical therapy available for CU, a systematic and thorough approach to identify a treatable cause in difficult CU patients is warranted. (Allergy Asthma Proc 27:90–95, 2006)

Over the years, research into the pathophysiology and cause of chronic urticaria (CU) has produced few major breakthroughs. Consequently, in many patients, no cause can be identified, often leaving them frustrated, with symptomatic treatment only. The medications required to control symptoms are marginally effective and frequently have bothersome and sometimes dangerous side effects; therefore, the search for a cause in each patient is crucial. This review will focus on possible underlying mechanisms and some of the etiologic factors that have been identified in an attempt to augment the understanding of this frustrating affliction and, hopefully, help the clinician better manage these difficult patients.

Urticaria itself has a long history, having been referred to by the Chinese as far back as the 7th century¹ and described by Heberden in the 18th century.² Although there are few epidemiologic studies of the

prevalence of CU, Greaves estimated that it affects up to 0.1% of the population including both adults and children.³ Thus, it is a significant and relatively frequent health problem. Although it is rarely fatal, it has significant adverse effects on quality of life, as discussed by Weldon in this symposium and others.⁴ CU is defined as frequent or daily hives persisting for >6 weeks.⁵ The duration is extremely variable, dependent especially on success of finding a cause. Estimates suggest an average duration of 3–5 years,³ which is little consolation to most patients. Tobi *et al.* found that CU lasted >1 year in 70% of patients and >5 years in 14% of patients.⁶ The physical urticarias such as cholinergic urticaria often are included in reviews of CU but will not be discussed here, despite an association of delayed pressure urticaria with CU, which often shares a parallel course.⁷

PATHOPHYSIOLOGY

The characteristic clinical lesion of CU, similar to the more common acute urticaria, is the hive. In most cases the individual hives last 2–3 hours, but in some of the more severe patients, especially those with urticarial vasculitis, they may persist for up to 48 hours and sometimes leave residual ecchymotic areas.⁸ Up to 40% of CU patients have associated angioedema.⁹ The underlying pathophysiology is similar to hives, however. Both hives and angioedema are produced by the re-

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lease of mediators, predominantly histamine, from cutaneous mast cells. However, angioedema is a deeper lesion. The histamine induces the wheal, or swelling, through increasing capillary permeability, the erythema by vasodilatation, and the itch through stimulation of the irritant receptors. Mathews described this mast cell mediator release phenomenon as the "final common pathway" through which all precipitating factors act.⁵

There are several described mechanisms causing mediator release from cutaneous mast cells,⁵ and given the high frequency of "idiopathic" CU, there are likely additional ones, which we still have not discovered. Some of these processes are more theoretical than others. The "classic" activation pathway is *via* antigen bridging of specific immunoglobulin E (IgE) bound to a receptor on the surface of the cutaneous mast cell. This type of reaction results from ingestion of drugs and foods to which the patient has developed specific IgE. It is seen more commonly in connection with acute urticaria, but, as discussed later, it is sometimes associated with CU. Products of complement activation, C3a and C5a, often referred to as anaphylatoxins, also can activate mast cells.⁹ This is likely the process associated with immune complex disease such as serum sickness, systemic lupus erythematosus, and some chronic infections like hepatitis. There are other, more recently described, autoimmune phenomena, including antireceptor and anti-IgE antibodies, which may function through complement activation,¹⁰ but this remains to be clarified.

A variety of compounds including drugs, peptides and vasoactive amines are capable of releasing mediators from cutaneous mast cells through mechanisms still unknown. The most commonly used compounds in clinical studies of *in vivo* thresholds are codeine and compound 48/80.^{11,12} Studies of substance P, endorphins, enkephalins, endogenous peptides such as gastrin, vasoactive intestinal peptide, and somatostatin, have shown their ability to release histamine from cutaneous mast cells at concentrations slightly above physiological levels.¹³⁻¹⁶ This property of these endogenous compounds to activate cutaneous mast cells becomes more significant when there is a decrease in the threshold of mast cell activation. Indeed, as discussed in the following paragraphs, information generated over the last several years suggest that this may be the case in a certain group of CU patients, especially those with "autoimmune" urticaria.

The presence of autoimmunity in a significant number of CU patients was initially suggested by Gratten's demonstration of skin reactivity to the injection of the patient's own serum, autologous serum skin test (ASST).^{17,18} There have been several studies of the actual serum components responsible for this reactivity. In summary, immunoassays have shown antibod-

ies to the α -subunit of the IgE receptor on basophiles in 30–40% of CU patients and to IgE in 5–10% of patients. These have, to date, not correlated well with functional assays, such as histamine release or the ASST.^{9,10,19-27} This also has been shown in children with CU.²⁸⁻²⁹ The origin of these phenomena and their clinical significance remain as a major area for additional study. The association of autoimmune thyroid disease with CU, first described by Leznoff in 1983,³⁰ has proved to be a more fruitful area for clinical application. The suppression of thyroid activity and possibly the autoimmune process have resulted in disease remission in several CU patients and will be discussed later under causes.³¹⁻³³ Consequently, $\geq 30\%$ of CU patients, those having associated abnormal immune activity, are classified as having "autoimmune urticaria."

The abnormal activation of the immune system in CU patients has significant implications for understanding the underlying pathophysiology of CU. Natbony *et al.*³⁴ first indicated that the perivascular infiltrate seen in many CU patients is composed primarily of mononuclear cells. Mekori *et al.* characterized this infiltrate as predominantly composed of T lymphocytes, specifically T4, helper cells.³⁵ Recently, Caproni *et al.* biopsied lesions induced in CU patients by intradermal injection of autologous serum (ASST). They found a mixed Th1/Th2 lymphocyte response, neutrophil infiltration, and increased activity of the chemokine system. Inflammatory cells and chemokine up-regulation also were found in clinically uninvolved skin, suggesting widespread cutaneous immune hyperactivity.³⁶

Abnormal histamine release is also a characteristic of CU. Kern and Lichtenstein showed decreased histamine releasability from peripheral blood leukocytes in CU patients.³⁷ Kaplan *et al.*, using the skin blister technique, found increased levels of histamine in lesional skin.³⁸ Phanuphak *et al.*, examining extracts from skin biopsies, found elevated histamine levels in lesions and also in normal skin.³⁹ Several studies were then reported assessing mast cell releasability, or threshold of release. Bedard *et al.*, studied CU patients using the skin chamber technique. They found an increase in histamine release in nonlesional skin,⁴⁰ and Cohen and Rosenstreich showed an increased reaction to injected codeine in nonlesional skin.⁴¹ Thresholds of release returned to normal when the CU went into remission as reported by Jacques *et al.*,⁴² further supporting the clinical relevance of altered thresholds. Using a modified basophil histamine release assay, Claveau *et al.* identified histamine-releasing activity in the skin blister fluid from active CU patients, particularly in nonlesional skin.⁴³ They also showed that although histamine-releasing activity was increased in the skin, it was decreased in the peripheral blood,⁴⁴ confirming Lichtenstein's earlier observation. Studies of hista-

mine-releasing factors have identified a heterogeneous group of compounds with various immunologic functions, but all were capable of activating mast cells or basophils.⁴⁵ Some of these are IgE dependent and others are IgE independent.⁴⁶ Thus, histamine-releasing activity has been associated with chemokines and cytokines released on lymphocyte activation, potentially tying the presence of the lymphocytic perivascular infiltrates often seen in the skin of CU patients with a lowered cutaneous mast cell releasability threshold. To then associate this lowered releasability to the clinical picture of the CU patient with constant and persistent hives, we should refer back to the variety of endogenous peptides and chemicals that are capable of activating mast cells. An active immunologic or "autoimmune" process might release histamine-releasing factors, which are capable of lowering the threshold of release of the cutaneous mast cells. This would render them more susceptible to release by endogenous substances. The threshold then returns to normal when the immunologic process remits, resulting in the resolution of the hives.

ETIOLOGIES

The identification of causative factors in most patients with CU is a formidable task. Finding an underlying cause and treating or eliminating it, clearly, is far superior to marginally effective and potentially dangerous pharmacologic therapy. Unfortunately, most reviews on the subject fail to identify a cause in the majority of patients. This leaves a high percentage of patients frustrated and uncomfortable. There are some barriers to identification of causative factors. The presence of several coexisting factors frequently makes it difficult to isolate and identify any one of them. This may be the case with multiple drug or food sensitivities and the coincident occurrence of potentiating stimuli to mediator release, such as seen in food-induced exercise anaphylaxis,⁴⁷ and delayed pressure urticaria caused by food allergy.⁴⁸ The nonspecific exacerbation of hives by drugs such as nonsteroidal anti-inflammatory drugs and narcotics also may cloud the assessment. Reviews, which indicate that food allergy is an unlikely cause of CU in adult patients,^{49,50} can cause us to miss that occasional patient who is reacting to common food ingestion. Personally, I take a very systematic approach to elimination of potential causative factors using aggressive drug elimination, food skin testing, and elimination diets along with limited laboratory testing. I frequently see referral patients who have "tried everything," are very frustrated, and appreciate a logical assessment. We can be heroes to any patient in whom a cause can be identified and elimination results in a successful outcome. For those, it is worth the "hunt."

Typical of the classic IgE-mediated causes of CU are drugs, foods, and some infections.¹ Although, on the surface, drug issues appear to be relatively straightforward, some CU patients are on multiple life-supporting medications and withdrawal may have serious health consequences. These situations require careful withdrawal, tedious substitutions, and close cooperation with the treating physicians. With the development of all the new, genetically engineered maintenance biologicals, this type of reaction may become more common. Another area for investigation is the common and, often, surreptitious use of over-the-counter medications, supplements, vitamins, and alternative medical preparations. Patients may not offer information about such exposures unless specifically addressed. It would not be unusual for the sudden resolution of CU after discontinuation of these products.

Food allergy has long been a controversial topic related to CU. It is commonly seen as a cause of acute allergic reactions and sometimes is associated with CU in children. However, in most reviews of either CU or food allergy in adults, it usually is downplayed as a causative factor.^{49,50} Although it is not common, there are some adult patients in whom allergies to "ubiquitous" food antigens such as wheat, soy, corn, yeast, and rice can cause chronic hives. These foods are staples of most diets. Traditional elimination diets may not exclude a rice allergy, and rice is a staple in many Asian diets. Interestingly, in my experience, food allergies can develop at any age, having seen an Asian woman who developed CU from the onset of a rice allergy at the age of 70 years. I have been using food skin tests or radioallergosorbent tests to develop a palatable and confirmed negative elimination diet, which I then implement for 2 weeks. The absence of improvement by the end of this period excludes food as cause of CU in that patient. The relation of preservatives and additives to CU has been a controversial topic for years, but to date, has not been well proven.⁵¹ These also could be excluded on an elimination diet to assess their relevance.

Infection has been included in most reviews of CU, although this is uncommonly identified. Parasitic infection was the classic one described, but successful eradication rarely resulted in remission of the hives. CU has been associated with *Helicobacter pylori* infection, but the etiologic relevance still is in question.⁹ Anecdotal reports of resolution of CU after treatment of fungus infection such as onychomycosis provide additional avenues of treatment to explore.

There are miscellaneous causes and disease associations with CU, which have no discernable common mechanisms. CU has been associated with malignancies, particularly of the hematologic system.^{1,3,5} Associations with *Helicobacter* infection gastritis, atrophic

gastritis with low B12 levels, have been described.⁵² Endocrine disorders including hyperparathyroidism, hyperthyroidism, and hypothyroidism have been reported as potential causes, because treatment resulted in resolution of the coincident CU.³³ One report described a patient with CU and hypercalcemia,⁵³ in whom hives resolved after the removal of a parathyroid adenoma. Pruritus or urticaria may be the presenting symptoms of thyrotoxicosis and have been reported to resolve after treatment of the thyroid disease with antithyroid medication⁵⁴ or thyroid ablation.⁵⁵ Thyroid disease in CU patients is a more common occurrence than has been appreciated. Small and Lerman found 6 of 154 patients with CU with hyperthyroidism.⁵⁶ Leznoff *et al.* reported 17 or 12% of 140 consecutive patients with CU had elevated levels of thyroid microsomal antibodies.³⁰ The relation of thyroid autoimmunity to CU will be discussed in more detail later in this study.

Urticarial vasculitis is an uncommon variant of CU, which combines the clinical manifestations of CU with the histopathological findings on skin biopsy of cutaneous vasculitis, specifically leukocytoclastic vasculitis. It is an uncommon disease and, if the strict definition of vasculitis is followed, it comprises <5% of CU patients. Many patients have additional systemic symptoms such as arthralgias, arthritis, and abdominal pain and, occasionally, have renal involvement. Hypocomplementemia, with antibodies to C1q is found in some of these patients, and depressed levels of C1q and reductions in CH50, C2, and C4 are seen also. Immune complexes have been found in the circulation of 30–75% of the urticarial vasculitis patients, and on skin biopsy, vessel wall deposition of immunoreactants and complement components suggest immune complexes play a significant role in this disease. Some of these cases have been associated with connective tissue disease like systemic lupus erythematosus and others with chronic hepatitis B or C infections.⁸ Malignancies and gastrointestinal diseases also have been associated with CU, but the underlying mechanisms have not been determined.¹

The finding of abnormal immunologic phenomena in a significant number of patients with CU has led to the addition of the term, “autoimmune urticaria,” to describe a subclassification of CU. A significant number of these patients are positive on ASST, have antibodies to the α -subunit of the basophil IgE receptor, and some have antibodies to IgE. However, the results of these tests often do not correlate with each other in the individual patient.^{9,10} Furthermore, their clinical significance still is unclear. Some authors suggest that patients with “autoimmune” urticaria have a more prolonged and severe course, justifying more aggressive therapy.^{9,10,57} The presence of autoimmune thyroiditis in patients with CU may be a more clinically

relevant autoimmunity finding³³; however, controlled studies supporting this association are lacking. The incidence of antithyroid antibodies, including antiperoxidase, antimicrosomal, and antithyroglobulin antibodies is variable in CU patients. Although several patients with thyroid autoantibodies also have positive ASSTs, antireceptor, and anti-IgE antibodies, Fusari *et al.* found that the latter persisted after the urticaria resolved, further calling into question their functional role.⁵⁷ Fourteen of the 17 CU patients reported by Leznoff with positive thyroid microsomal antibodies initially were euthyroid. In five of seven of these patients treated with levothyroxine, their CU improved or resolved.³⁰ Rumbyrt *et al.* reported a group of 10 patients with CU. Seven had either positive thyroglobulin and/or thyroid microsomal antibodies. All were euthyroid by thyroid function testing. Two of these were previously hypothyroid and were maintained at a euthyroid state with thyroid hormone replacement. The urticaria in the seven patients with thyroid autoantibodies, but not those without, resolved on suppressive doses of Synthroid (Abbot Laboratories, North Chicago, IL). Hives resolved in one patient who was treated single blindly with Synthroid and placebo, only on the hormone suppression regimen and not on placebo. The goal of treatment is to maximally suppress thyroid-stimulating hormone without rendering the patient clinically hyperthyroid, although, in many patients, the urticaria remits much before this level is reached. This requires frequent monitoring of patients for clinical indicators of hyperthyroidism such as tachycardia, tremor, sleeplessness, palpitations, and diarrhea. The urticaria usually resolves within 2 weeks of initiation of adequate treatment, although in more severe cases and recurrent urticaria after cessation of previous suppressive therapy, response may take longer and requires perseverance of both physician and patient. The optimum duration of treatment has not been well studied, but in this author's experience, most patients maintain a sustained remission after 3–6 months of treatment at which point hormone treatment can be tapered and discontinued.³³ Although it is clear that some patients with CU remit on thyroid suppression, the underlying immunologic mechanisms are still unclear. Frequently, thyroid autoantibody levels do not parallel clinical course, and this author has treated two euthyroid CU patients with a strong family history of thyroid disease, without detectable thyroid autoantibodies, in whom the urticaria remitted on thyroid suppression. Without question, more controlled studies of treatment of this entity are needed. Because, in this case, the pathophysiology is still not defined, it is open to speculation. Theoretically, then, I would suggest that thyroid gland inflammation plays a central role in the initiation and propagation of this disease. The initiating factors may be viral, autoimmune, or

other infections. Bacos *et al.*⁵⁸ found an increased incidence of *H. pylori* infection in their CU patients with thyroid autoimmunity. They suggested that *H. pylori* might produce an antibody response that cross-reacts with thyroid components, triggering the autoimmune reaction. As a result of thyroid inflammation and cell disruption, ordinarily sequestered antigens are exposed to the immune system inducing an immune response as previously reviewed. Given the histopathology and the absence of correlation between antibody levels and clinical disease, the essence of the immune response more likely involves the cell-mediated immune system. The local activation of the immune system then induces lowered cutaneous mast cell releasability thresholds inducing mediator release to a whole range of endogenous compounds, as discussed earlier. The clinical result is persistent hives. Theoretically, thyroid suppression treatment lowers thyroid-stimulating production, putting the gland at rest; reducing activity, inflammation, and antigen release; and lowering immune stimulation. The pathophysiological result, which ultimately results in remission of the CU, is an elevated cutaneous mast cell releasability threshold. Additional factors may influence this process. Takeoka *et al.* reported elevation of autoantibody levels in patients with Grave's disease after seasonal allergic rhinitis.⁵⁹ There also might be other subclinical autoimmune processes, which induce similar immune activation leading to CU. An example suggesting this comes from a report by Mete *et al.* of reduced levels of B12 and positive antiparietal cell antibodies in a group of CU patients.⁵² Pernicious anemia has also long been associated with autoimmune thyroid disease. We have just scratched the surface of autoimmunity as a cause of CU. Although the presence of thyroid autoantibodies in the normal population is estimated at 3–6%,⁶⁰ routine testing for these antibodies is warranted in most CU patients. If they are found, aggressive therapy is worthwhile, especially in a disease where nonspecific suppressive therapy often is unsatisfactory and fraught with side effects.

In conclusion, although CU is a relatively common affliction, it is surprising how little we know about pathophysiology and etiology. This problem translates into a high percentage of "idiopathic" diagnoses. Nevertheless, the key to successful management and outcomes is still the identification of a treatable cause. This requires patience and a systematic, thorough, and thoughtful evaluation. The reward for success is well worth the effort.

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