Chronic Urticaria: An Evolving Story

Jonathan A. Bernstein MD

Department of Internal Medicine, Division of Immunology/Allergy Section, University of Cincinnati College of Medicine, Cincinnati, OH, USA

Key words: urticaria, physical hives, autologous serum skin test, antihistamines, pruritis

IMAJ 2005; 7: 774–777

Urticaria is defined as intense, itching welts caused by allergic reactions to internal and external agents. The word "urticaria" is derived from the Latin word *urtica*, which means "nettle." Nettles refer to any plant from the genus U*rtica*, which are tooth-leaved plants covered with hairs capable of secreting a stinging fluid that immediately affects the skin on contact [1]. Interestingly, nettles were used during ancient times as a treatment for paralysis [1]. Urticaria is characterized as raised, pink/erythematous skin lesions that are markedly pruritic. Lesions range from a few millimeters in size to several centimeters and may coalesce. An important characteristic of urticaria is that they are evanescent, meaning that old lesions vanish as new ones appear during a span of 24 hours. Typically, urticarial lesions leave no scarring and are generally worsened by scratching. Any area of the body may be involved. However, the most commonly affected regions are the perioral and periorbital regions, tongue, genitalia and extremities [2].

To better understand urticaria, it is important to be familiar with the triple response of Lewis [3]. This phenomenon refers to the characteristic wheal, erythema and itching sensation associated with hives. Erythema is primarily due to capillary and venule dilatation, which is further exacerbated by an axonal reflex mechanism. The edema associated with the wheal is due to increased capillary permeability resulting in extravasation of fluid from the blood vessel. Finally, pruritus occurs through a neuronal reflex mechanism. When the bioactive mediator histamine stimulates the histamine receptor, the itch impulse travels through C-fiber neurons to the lateral spinothalamic tract, up through the brainstem into the thalamus. This neuroreflex mechanism can also be triggered by a variety of other mediators such as neuropeptides [3].

The predominant cell types in the histopathology of chronic urticaria consist of lymphocytes that express HLA-DR antigens, which are arranged perivascularly [4]. With special staining techniques increased numbers of mast cells can be seen. Typically there is no evidence of vascular damage, nuclear debris or red cell extravasation. Some forms of urticaria exhibit predominantly neutrophils within the capillary and post-capillary venular walls without structural damage. This is thought to represent an intermediate histopathologic form of urticaria that differentiates "ordinary" urticaria from urticarial vasculitis [4]. Studies have demonstrated that spontaneous urticarial wheals have moderate expression of E-selectin, intracellular adhesion molecule-1 on vascular endothelial cells, and vascular cell adhesion molecule-1 on perivascular cells. This observation would explain the increased migration of inflammatory cells into the epidermal and dermal regions [5].

The prevalence of urticaria is estimated to occur in 15–23% of the population. Up to 40% of patients who have chronic urticaria for more than 6 months will still have urticaria 10 years later, although they may have hive-free periods of remission [4]. Approximately 40% of patients with chronic urticaria have angioedema. Acute urticaria refers to hives lasting less than 6 weeks [2]. An underlying inciting cause may be identified in approximately 15–20% of cases. However, most patients present with chronic urticaria that has persisted for longer than 6–8 weeks and in less than 5% can an underlying cause be identified. Therefore, it is not surprising that the most common cause of urticaria is idiopathic [2]. The classification of hives also includes the physical urticarias and urticarial vasculitis, the latter representing less than 1% of all urticarial cases [5]. Physical urticarias include symptomatic dermatographism, delayed pressure urticaria, cold urticaria, aquagenic urticaria, solar urticaria, cholinergic urticaria and vibratory angioedema/urticaria [5].

An immunologic mechanism is most often responsible for acute urticaria when a cause is identified. Causes include a spectrum of foods and drugs, insect sting reactions, transfusion reactions and, more rarely, contactants or inhalants. In general, food-related causes are responsible for less than 1% of reactions in adults and approximately 3–5% of reactions in children. In contrast, non-immunologic mechanisms are more frequently implicated in chronic urticaria when a cause is identified [6].

There are several hereditary forms of hives induced by physical factors such as cold, heat and vibration. Other hereditary causes of hives include porphyria, C3b inactivator deficiency, vasculitis, neoplasms, infections, endocrine disorders, and certain drugs. For instance, aspirin and non-steroidal anti-inflammatory drugs may exacerbate hives in up to 30% of cases [4]. One question always asked by patients is whether psychological conditions such as anxiety cause hives. Currently, this is considered to be more myth than fact. While hives are very anxiety

provoking, there is no evidence to support anxiety as a cause for hives [4].

Table 1 lists the features of physical urticaria [4]. Most of these disorders occur at or after the age of 20 until midlife. However, cold and cholinergic urticaria can occur as early as age 10. Many forms of physical hives can be transferred through serum to naive individuals [5]. This observation was demonstrated years ago, prior to the discovery that infectious agents are transmitted between individuals. These "transfer factors" in serum have yet to be well defined [5]. Of note, patients with secondary cold-induced urticaria may be more likely to form cryoglobulins, cryofibrinogen or cold agglutinins [5]. Patients who present with cold-induced urticaria should be screened for these abnormal proteins. A recent study investigating familial cold urticaria ("familial cold autoinflammatory syndrome"), an autosomal dominant disorder characterized by episodic urticaria, arthralgias, fever and conjunctivitis after exposure to cold temperatures, found that this disorder has the same genetic locus on chromosome 1q44 as Muckle-Wells syndrome, an autosomal dominant disorder characterized by periodic fevers, hives and sensorineural hearing loss [6]. This gene, identified as "cryopyrin," has significant homology to the N*od*2 gene implicated in Crohn's disease [6].

Table I. Features of physical urticaria*

Type	Age (yrs)	Clinical features	Angioedema	Diagnostic test
Dermatographism	20–50	Linear lesions	No	Light stroking of skin; + transfer factor
Cold (primary vs. secondary)	10–40	Itchy, pale lesions (5% have cryoglobulins)	Yes	5–10 minute ice-cube test; + transfer factor
Cholinergic (heat bumps)	10–50	Itchy, monomorphic pale or pink lesions	Yes	Exercise or hot shower; + transfer factor
Pressure	20–50	Large painful or itchy lesions	No	Dermographometer; application of pressure to skin
Solar	20–50	Itchy pale or red lesions	Yes	Irradiation by a solar simulator; + transfer factor

* From Ref. 4

Urticarial vasculitis is important to differentiate from chronic urticaria because the prognosis and treatment response can be quite different from conventional hives. Urticarial vasculitis has been associated with underlying connective tissue disorders such as systemic lupus erythematosus or infections such as hepatitis. This condition is clinically differentiated from urticaria in that the lesions are non-evanescent, lasting more than 24 hours. The hives are typically, but not always, associated with purpura and are hyperpigmented. Systemic signs and symptoms such as fever and pain may coexist [7]. Laboratory tests may reveal an increased sedimentation rate along with other acute-phase reactants and decreased complement levels. Biopsy is essential to differentiate urticarial vasculitis from chronic urticaria, as histopathology reveals leukocytoclasia and/or extravasation of red blood cells from blood vessels [7]. Treatment of urticarial vasculitis with antihistamines is not uniformly effective and more aggressive therapies may be necessary.

The relationship of chronic urticaria with underlying chronic disorders has been incompletely established in most cases. For example, the relationship of chronic urticaria with malignancies has long been suspected. To investigate this relationship, an epidemiologic study conducted by Lindelof et al. [8] evaluated 1,155 cases of chronic urticaria. A search of the Swedish Cancer Registry for malignancies in this chronic idiopathic urticaria population between the years 1958 and 1994 was simultaneously conducted. They calculated the expected number of malignancies for this population based on age and gender-standardized incidence data. A malignancy was identified in 36 of the subjects with CIU, which was less than the calculated number of 41 malignancies expected for the general population. They concluded that CIU was not statistically associated with malignancy [8]. Although it is generally believed that malignancy associated with CIU is rare, a link probably exists. For example, Schnitzler's syndrome is a well-defined disorder presenting in patients with CIU associated with an immunoglobulin M monoclonal gammopathy [9]. Other case studies have reported hives occurring with chronic myelogenous leukemia and other lymphoreticular malignancies [10,11].

The association of chronic urticaria and chronic hepatitis infection has also been investigated. Case reports have identified acute hives occurring in the presence of hepatitis A infection. A study conducted in 1983 reported hepatitis B viral antigen in 2 of 85 individuals with CIU [12]. Based on this one study, it was concluded that hepatitis B infection was associated with chronic urticaria. However, subsequent reports did not find a significant relationship between hives and hepatitis A, C or G infection [13]. Chronic urticaria has also been linked to parasitism. A*nisakis simplex* is a cephalopodes parasite [14]. Ingestion of these larvae was found to cause urticaria, angioedema, erythema, bronchospasm and anaphylaxis. Interestingly, specific IgE to this parasite was found in subjects after chronic ingestion of these larvae [15]. There is still ongoing debate as to whether this condition represents a true parasitic infection versus a food allergy to the A*nisakis simplex* larvae commonly found in fish [16].

More recently, chronic urticaria has been associated with H*elicobacter pylori* infection. Several studies have reported that CIU patients infected with H. *pylori* had total or partial amelioration of their hives after they were treated with triple therapy consisting of amoxicillin, clarithromycin and a proton pump inhibitor [17–22]. This relationship is not yet widely accepted by investigators.

The relationship between chronic urticaria and autoantibodies has been the subject of intense investigation over the past two decades. Early reports of increased thyroid autoantibodies in CIU patients suggested an association between autoantibod-

CIU = chronic idiopathic urticaria
Ig = immunoglobulin

ies and hives. This observation was more commonly reported for patients with Hashimoto's thyroiditis and, to a lesser extent, Graves' disease [2]. However, it remains unclear whether identification of thyroid autoantibodies represents a parallel abnormality reflecting an underlying autoimmune process or is functionally related to chronic urticaria. One study compared the sera from 25 CIU patients with that from 75 healthy subjects for a litany of autoantibodies [23]. Of the 25 CIU patients, one had inflammatory bowel disease and one had multiple myeloma. The only autoantibodies that were statistically more common in the CIU population were thyroid peroxidase and rheumatoid factor. In general, the authors concluded that non-specific autoimmunity was not present in their population of CIU patients [23].

More recently, investigators found that up to 40% of patients with chronic urticaria may make IgG autoantibodies to either Fcε RI α-subunit (35–40% of subjects) or to IgE (5–10% of subjects). Studies have demonstrated that the mechanism of autoimmune induced chronic urticaria is due to cross-linking of the autoantibody IgE receptors or the IgE molecule on the Fcε RI receptor, resulting in release of bioactive mediators such as histamine. Several investigators have confirmed this observation using a number of experimental designs [24,25]. Skin testing to autologous serum was previously shown by Grattan et al. [26] to be a useful and simple method for identifying the presence of autoantibodies to Fcε RI α-subunit or IgE in CIU patients. However, this test is non-specific as it may also reflect the presence of a not yet defined histamine-releasing factor [26]. The functionality of these autoantibodies remains to be fully elucidated. Recently, we treated a 45 year old African American female with a 20 year history of CIU unresponsive to H1- and H2-antgonists and other anti-inflammatory agents but well controlled on daily prednisone 35 mg twice a day for over 13 years. Chronic use of corticosteroids resulted in a 45.5 kg weight gain and other chronic corticosteroid-induced side effects. Intracutaneous testing to autologous serum revealed an 8x10 mm wheal/flare reaction. Treatment with intravenous cyclophosphamide was initiated in an attempt to eradicate autoantibody-producing B lymphocyte clones. This approach has previously been used successfully in other autoantibody-mediated disorders such as type 2 acquired angioedema and factor VIII deficiency. The total dose of cytoxin used represented 20% of the standard dose administered for systemic chemotherapy. This treatment was only undertaken after the patient failed all other forms of therapy. After 7 months of treatment, there was complete clinical remission of hives and the prednisone could be discontinued. Repeat intracutaneous testing to autologous serum after completion of cytoxin therapy was negative. The patient has remained hive-free for over 1 year after treatment. This index case may have significant therapeutic implications in the treatment of autoantibody-induced chronic urticaria refractory to conventional treatment [27].

Evaluation of patients with chronic urticaria requires a thorough history and physical examination. Evidence of dermatographism or other forms of physical hives needs to be excluded. A limited laboratory assessment should include a complete blood count with differential, a sedimentation rate, thyroid-stimulating hormone, liver function tests and urinalysis [2,4,5]. Refractory cases of hives may necessitate checking the C4 level, thyroid autoantibodies, H. *pylori* antibodies, and a hepatitis screen. If the hives are non-evanescent, a skin biopsy including a hematoxylin & eosin stain and direct immunofluorescence should be performed. Given the high incidence of autoantibodies in this population, skin testing to autologous serum should be considered. It is important to emphasize that allergen skin testing to common seasonal and perennial allergen inhalants is not indicated in the primary evaluation of hives unless concomitant upper and lower respiratory symptoms exist suggestive of allergic rhinitis and/or asthma [2,4,5].

The Joint Task Force – a committee including members from the American Academy of Allergy, Asthma & Immunology and the American College of Allergy, Asthma and Immunology – has published practice parameters to be used for the evaluation and treatment of CIU [28]. Treatment of CIU requires an algorithmic approach to identify the medication or combination of medications that will completely prevent the occurrence of hives. One should begin with agents that have fewer side effects since treatment is often prolonged. Each treatment trial should be for at least 2 weeks prior to changing or adding a medication. For severe cases of hives, treatment with oral corticosteroids is sometimes required to initially control the hives, followed by a slow taper to determine the effectiveness of the underlying primary treatment. Treatments for chronic urticaria include: class 1 H1 receptor antagonists (agents) (hydroxyzine, diphenyl-hydramine) or class 2 non- or low sedating antihistamines (fexofenadine, loratadine, desloratadine and cetirizine). H2 receptor antagonists, such as cimetidine, ranitidine or famotidine, may also be effective in a subpopulation of patients with CIU. It is important to note that 85% of histamine receptors are of the H1 type and approximately 15% of the H2 type. Medications that block both H1 and H2 receptor antagonists include doxepin. This medication also blocks muscarinic receptors. Certain agents have mast cell-stabilizing properties including oral albuterol and the antihistamine, azatadine. Case reports have noted that leukotriene-modifying agents such as montelukast, zafirlukast and zileuton may be helpful in the treatment of some patients with CIU [2]. We previously demonstrated that autologous serum skin test-positive individuals may respond better to combination cetirizine and zafirlukast compared to cetirizine alone [29].

For certain types of hives, selective treatments have been recommended. For example, patients with pressure-induced urticaria may benefit from treatment with calcium channel blockers (nifedipine) and azatadine. Cold-induced urticaria responds well to cyproheptadine, which blocks H1 and serotonin receptors. Patients who have neutrophilic infiltrates on skin biopsy may respond better to dapsone or colchicine. L-thyroxine has been shown to be helpful in controlling hives in patients with thyroid autoantibodies [2,4,5]. Finally, controlled studies found that stanozolol (an androgen) is effective for treating hives; its mechanism of action is believed to be the increase in serum proteases that are low in some patients with CIU [30]. Other

agents considered as alternative treatments for chronic hives include cyclosporine, gold, hydroxychloroquine and methotrexate [2,4,5]. Patients with autoantibody-induced chronic urticaria refractory to conventional treatments should be considered for treatment with cyclophosphamide, plasmapheresis or intravenous immunoglobulins [2,4,5].

The natural course and prognosis of chronic urticaria is variable. One study investigated 220 adults with CIU prospectively for 1 to 3 years. They found that after 1 year 35% of patients were free of all symptoms and 30% had decreased symptoms. After 3 years 47% of these patients had spontaneous remission compared to only 16% of those who also had a component of physical urticaria. The authors concluded that the prognosis for spontaneous remission in chronic urticaria is reasonable with the exception of the subgroup of patients who had a physical component to their urticaria [31].

In conclusion, chronic urticaria is a debilitating disorder with a variable clinical course, but proper evaluation and treatment can result in very successful clinical outcomes. Research of chronic hives has progressed significantly over the past decade. However, there is a great deal of work that needs to be done in order to gain a better understanding of the immunopathogenesis and treatment of this disorder.

References

1. Webster's Dictionary.
2. Kaplan AP. Chronic urticaria and angioedema. N *Engl* J *Med* 2002;346:175–9.
3. Kaplan AP. Urticaria and angioedema. In: Middleton E, Reed CE, Ellis EF, Adkinson NF, Yunginger JW, Busse WW, eds. Allergy: Principles and Practice. 4th edn. New York: Mosby-Year Book, 1993:1553–80.
4. Greaves MW. Chronic urticaria. N *Engl* J *Med* 1995;332:1767–72.
5. Greaves MW. Chronic urticaria. J *Allergy Clin Immunol* 2000;105: 664–72.
6. Hoffman HM, Mueller JL, Broide DH, Wanderer AA, Kolodner RD. Identification of a gene for familial cold urticaria. N*at Genet* 2002;29:301–5.
7. Fox RW. Chronic urticaria: mechanisms and treatment. A*llergy Asthma Proc* 2001;22:97–100.
8. Lindelof B, Sigurgeirsson B, Wahlgren CF, Eklund G. Chronic urticaria and cancer: an epidemiological study of 1155 patients. B*r* J *Dermatol* 1990;123(4):453–6.
9. Lim W, Shumak KH, Reis M, et al. Malignant evolution of Schnitzler's syndrome – chronic urticaria and IgM monoclonal gammopathy: report of a new case and review of the literature. L*euk Lymphoma* 2002;43(1):181–6.
10. Alonso R, Cistero-Bahima A, Enrique E, Besses C. Chronic urticaria associated with chronic myelomonocytic leukemia. J I*nvestig Allergol Clin Immunol* 2002;10(6):380–1.
11. Brown EB, Hermance WE, Choi YC. Serum immunoglobulin M in chronic urticaria. A*nn Allergy* 1974;33(6):331–6.
12. Vaida GA, Goldman MA, Bloch KJ. Testing for hepatitis B virus in patients with chronic urticaria and angioedema. J *Allergy Clin Immunol* 1983;72(2):193–8.
13. Cribier BJ, Santinelli F, Schmitt C, Stoll-Keller F, Grosshaus E. Chronic urticaria is not significantly associated with hepatitis C or hepatitis G infection: a case-control study. A*rch Dermatol* 1999;135(11):1335–9.
14. Scala E, Giani M, Pirrotta L, et al. Occupational generalized urticaria and allergic airborne asthma due to anisakis simplex. E*ur* J *Dermatol* 2001;11(3):249–50.
15. Daschner A, Alonso-G, Markomez A, et al. Gastroallergic anisakiasis: borderline between food allergy and parasitic disease: clinical and allergologic evaluation of 20 patients with confirmed acute parasitism by Anisakis simplex. J *Allergy Clin Immunol* 2000;105:176–81.
16. Gracia-Bara MT, Matheu V, Zubeldia JM, et al. Anisakis simplex-sensitized patients: should fish be excluded from their diet? A*nn Allergy Asthma Immunol* 2001;86(6):679–85.
17. Di Campli C, Gasbarrini A, Nucera E, et al. Beneficial effects of Helicobacter pylori eradication on idiopathic chronic urticaria. D*ig Dis Sci* 1998;43:1226–9.
18. Wedi B, Wagner S, Werfel T, Manns MP, Kapp A. Prevalence of Helicobacter pylori-associated gastritis in chronic urticaria. I*nt Arch Allergy Immunol* 1998;116(4):288–94.
19. Hizal M, Tuzun B, Wolf R, Tuzun Y. The relationship between Helicobacter pylori IgG antibody and autologous serum test in chronic urticaria. I*nt* J *Dermatol* 2000;39(6):443–5.
20. Gala Ortiz G, Cuevas Agustin M, Erias Martinez P, et al. Chronic urticaria and Helicobacter pylori. A*nn Allergy Asthma Immunol* 2001;86(6):696–8.
21. Hidvegi B, Gonzalez-Cabello R, Temesvari E, et al. The effect of heat-inactivated Helicobacter pylori on the blastogenic response of peripheral blood mononuclear cells of patients with chronic urticaria. I*nt Arch Allergy Immunol* 2001;126(2):167–72.
22. Sakurane M, Shiotani A, Furukawa F. Therapeutic effects of antibacterial treatment for intractable skin diseases in Helicobacter pylori-positive Japanese patients. J *Dermatol* 2002;29(1):23–7.
23. Ryhal B, DeMera RS, Shoenfeld Y, Peter JB, Gershwin ME. Are autoantibodies present in patients with subacute and chronic urticaria? J I*nvestig Allergol Clin Immunol* 2001;11(1):16–20.
24. Hide M, Francis DM, Grattan CEH, 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;328:1599–604.
25. Ferrer M, Kinet J-P, Kaplan AP. Comparative studies of functional and binding assays for IgG anti-Fcε RIα (α-subunit) in chronic urticaria. J *Allergy Clin Immunol* 1998;101:672–6.
26. Grattan CEH, Wallington TB, Warin RP. A serological mediator in chronic idiopathic urticaria: a clinical immunological and histological evaluation. B*r* J *Dermatol* 1986;114:583–90.
27. Bernstein JA, Garramone SM, Lower EG. Successful treatment of autoimmune chronic idiopathic urticaria with intravenous cyclophosphamide. A*nn Allergy Asthma Immunol* 2002;89:212–14.
28. Wanderer AA, Bernstein L, Goodman DL, et al. eds. The Diagnosis and Management of Urticaria: A Practice Parameter. In: Annals of Allergy, Asthma & Immunology, 2000;85(6):521–44.
29. Bagenstose SE, Levin L, Bernstein JA. The addition of zafirlukast to cetirizine improves the treatment of chronic urticaria in patients with positive autologous serum skin test results. J *Allergy Clin Immunol* 2004;113:134–40.
30. Parsaad D, Pandhi R, Juneja A. Stanozolol in chronic urticaria: a double blind, placebo controlled trial. J *Dermatol* 2001;28(6): 299–302.
31. Kozel MM, Mekkes JR, Bossuyt PM, Bos JD. Natural course of physical and chronic urticaria and angioedema in 220 patients. J *Am Acad Dermatol* 2001;45(3):387–91.

Correspondence: Dr. J.A. Bernstein, University of Cincinnati College of Medicine, 231 Albert Sabin Way ML#563, Cincinnati, OH 45267-0563, USA.
Phone: (1-513) 558-5533
Fax: (1-513) 558-3799
email: Jonathan.Bernstein@uc.edu