Current reviews of allergy and clinical immunology

(Supported by a grant fromAstra Pharmaceuticals, Westborough, Mass)

Series editor: Harold S. Nelson, MD

Chronic urticaria

Malcolm Greaves, MD *London, United Kingdom*

Chronic urticaria remains a major problem in terms of etiology, investigation, and management. It is important to identify patients in whom physical urticaria is the principal cause of disability. Once confirmed by appropriate challenge testing, no further investigation is required. Urticarial vasculitis (UV) is a major differential diagnosis of "idiopathic" urticaria (CIU). I perform biopsy of most patients in this category because UV cannot be considered confirmed in the absence of histologic evidence. Patients with confirmed UV need to be thoroughly investigated for paraproteins, lupus erythematosus hepatitis B and C, and inflammatory bowel disease. Of patients with CIU, a few (<5%) prove to have food additive reactivity confirmed by placebo-controlled challenge testing. There is no convincing evidence of the involvement of *Helicobacter pylori* or parasite infestation as a cause of chronic urticaria, although *H pylori* could have an indirect role. Recently it has become clear that 27% to 50% of patients with CIU have functional autoantibodies directed against the α-chain of the high-affinity IgE receptor or less commonly against IgG. These antibodies, whose involvement has now been independently confirmed in several centers, are identified by autologous serum skin testing and confirmed by histamine release studies or immunoblotting. Their removal (by intravenous Ig or plasmapheresis) or treatment by cyclosporine has proved highly beneficial in severely affected patients. However, the routine treatment of all CIU patients, irrespective of etiology, remains the judicious use of H_1 antihistamines. (J Allergy Clin Immunol 2000;105:664-72.)

Key words: *Chronic urticaria, immunology, allergy, urticarial vasculitis, idiopathic urticaria, intravenous Ig, itching, cold urticaria*

Recently, new light has been shed on the pathomechanisms of so-called chronic "idiopathic" urticaria (CIU), and this has in turn led to new approaches to diagnosis and, at least for some patients, treatments. However, it has to be admitted that, in many patients with chronic urticaria, the etiology still remains unclear despite our best efforts and these patients have to be managed symptomatically.

Abbreviations used

CIU: Chronic idiopathic urticaria
FcεRI: High-affinity receptor for IgE
UV: Urticarial vasculitis

CLINICAL FEATURES OF CHRONIC URTICARIA

The cardinal clinical features of urticaria that distinguish it from any other type of inflammatory eruption are the repeated occurrence of short-lived cutaneous wheals accompanied by redness and itching (Fig 1). Wheals are lesions ranging from a few millimeters to several centimeters in diameter, although if they run together and become confluent much larger plaques may occur. Individual wheals normally, by definition, last less than 24 hours, although there are exceptions. Wheals of the physical urticaria–delayed pressure urticaria may individually last for as long as 48 hours and the wheals of urticarial vasculitis (UV) by definition should last in excess of 24 hours. Urticarial wheals are generally paler than the bright red of the surrounding skin because of the compressing effect of dermal edema on the normally blood-engorged postcapillary venules. The surrounding skin may sometimes be conspicuously pale rather than red, giving the impression of a white halo. This phenomenon, more common in acute physical urticarias such as cholinergic urticaria and in acute allergic urticarias, is the result of a "steal" effect, increased arteriolar blood flow associated with the central wheal leading to deprivation of blood flow in the perilesional skin. Wheals may be round or irregular with pseudopodia.

Urticaria may occur anywhere on the skin, including the scalp, palms, and soles. Unlike angioedema, urticaria of the mucous membranes is rare, although the physical urticaria–cold urticaria may involve the tongue or palate.

The itch of urticaria is almost invariable, although some patients may have more intense pruritus than others. Qualitatively, the itching may be pricking or burning in quality. It is usually worse in the evening or nighttime[1] and is relieved by rubbing the skin rather than by scratching: heavily excoriated skin is rarely if ever a consequence of urticaria.

At least 50% of patients with chronic urticaria also have angioedema.[2] Angioedema can be defined as short-lived deep dermal and subcutaneous or submucosal edema. Like the wheals of urticaria, the swellings of angioedema normally last less than 24 hours, but large swellings tend to last longer. Disfiguring when they

From St John's Institute of Dermatology, St John's Hospital, United Medical and Dental School, London, United Kingdom.

Received for publication Dec 3, 1999; revised Jan 14, 2000; accepted for publication Jan 14, 2000.

Reprint requests: Malcolm Greaves, MD, St John's Institute of Dermatology, St John's Hospital, United Medical and Dental School, Lambeth Palace Road, London SE1 7EH, United Kingdom; fax 44 171 401 2008.

0091-6749/2000 $12.00 + 0 **1/1/105706**
doi:10.1067/mai.2000.105706

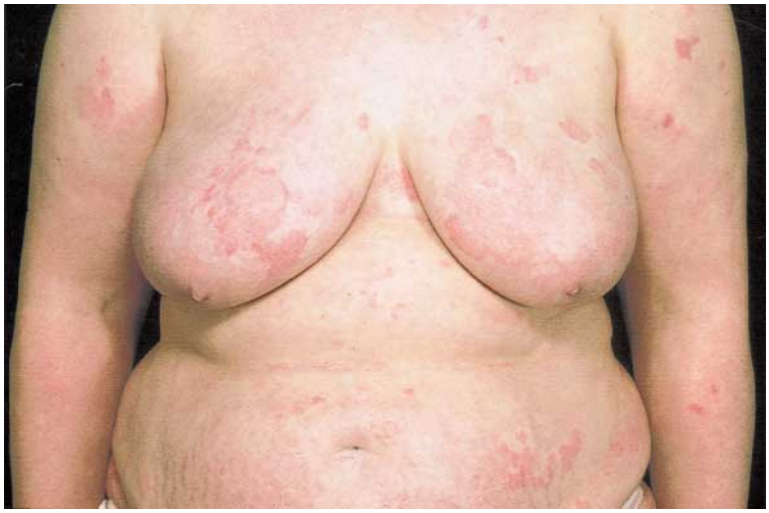

FIG 1. Chronic idiopathic urticaria.

occur in the skin, they can be extremely alarming and occasionally life threatening when they occur in the oropharynx. The swellings of angioedema are red or skin colored. Itching is less consistently associated with angioedema than with urticaria. Indeed, these swellings may not itch at all.

The classification of chronic urticaria, for the purposes of this discussion, is given in Table I.

PHYSICAL URTICARIAS

It is most important to distinguish the physical urticarias from CIU. This is because, if it turns out that a physical urticaria is the main cause of chronic urticaria in an individual, it almost invariably obviates the necessity for investigation beyond any challenge testing necessary to confirm the diagnosis. There are rare exceptions; for example, it is desirable to exclude the (rare) presence of plasma cryoproteins in patients with cold urticaria. However, it is my everyday experience that patients with physical urticarias are burdened with a costly host of unnecessary investigations and diet restrictions that shed no light whatever on the cause and do not influence the treatment of the disease.

The physical urticarias are characterized by the development of whealing and itching promptly after application of the appropriate physical stimulus. The exception is delayed pressure urticaria. A period of 2 or more hours usually elapses before whealing develops in response to applications of pressure to the skin. It is common for more than one physical urticaria to afflict a patient concurrently. For example, symptomatic dermographism and cholinergic urticaria frequently occur simultaneously. Characteristically the wheals of physical urticarias are transitory, lasting for only a few minutes or no more than an hour or 2 after removal of the provoking stimulus. Again, delayed pressure urticaria is an exception; wheals, often painful as well as itchy, last for 24 hours or more.

After whealing has been evoked and has subsided, the affected skin is frequently refractory to further provocation for a period ranging from a few hours to a day or 2 and this fact has been made use of in the management of some physical urticarias, including cold urticaria and solar urticaria.

We have published consensus guidelines for challenge testing in confirmation of the diagnosis of physical urticarias.[3] This is important because accurate characterization of a physical urticaria enables useful advice to be given to the patient regarding avoidance of symptoms, as well as for prognosis and treatment.

Only the more common physical urticarias will be detailed further here.

SYMPTOMATIC DERMOGRAPHISM (FACTITIOUS URTICARIA)

The diagnosis of symptomatic dermographism can be made by drawing the tip of a blunt-pointed instrument firmly across the skin. This causes an immediate linear red wheal that (in contrast to “ordinary” dermographism that can occur in a healthy person) manifests itching.

Any region of the body can be affected. The condition, which occurs at any age, runs on average a course of 2 to 3 years before resolving spontaneously. The wheals, which last for up to 30 minutes, fade, leaving no mark. Unlike urticaria pigmentosa caused by cutaneous mastocytosis (which also manifests dermographism—Darier’s sign), there is no increase in skin mast cell numbers. Rarely, symptomatic dermographism is a sequel of scabies, lasting for several weeks after successful treatment of this infestation. There is no association with systemic disease.

The cause is unknown, but passive transfer has successfully been carried out with patient serum and nonhuman primate skin as a recipient.[4] Although conceivably IgE, the identity of the transferable factor has yet to be positively established.

TABLE I. Classification of chronic urticaria

Physical urticaria
Symptomatic dermographism
Delayed pressure urticaria
Cold urticaria
Aquagenic urticaria
Solar urticaria
Cholinergic urticaria
Vibratory angioedema
CIU
Urticarial vasculitis*

* Mentioned for the sake of completeness, but not considered in detail in this account.

With use of an in vivo dermal perfusion method we[5] established many years ago that histamine released locally is a major mediator of symptomatic dermographism. Because the condition responds well to combined H_1 and H_2 antihistamines,[6] it seems likely that dermal mast cell–derived histamine is the main, if not the only, mediator of this physical urticaria. The transitory time course of the wheals and itch would also support this notion.

DELAYED PRESSURE URTICARIA

It is not generally appreciated how common delayed pressure urticaria is. Our results show that at least 40% of all patients with CIU have concurrent delayed pressure urticaria.[7] Indeed, it is doubtful if it ever occurs in isolation. This explains the frequency of wheals at local pressure sites (waistband, palms, soles, etc) in CIU. It also explains the poor response to H_1 antihistamines in some patients with CIU because delayed pressure urticaria is generally poorly responsive to this treatment.

Characteristically the wheals of delayed pressure urticaria occur 2 to 6 hours after application of pressure to the skin and last for more than 24 hours. These wheals are itchy or quite often painful, especially on the feet. They can be disabling, especially to a manual worker, and are often associated with arthralgia. The diagnosis is made by applying a dermographometer (a spring-loaded pen-like instrument calibrated to administer a range of pressures within a continuously variable range) perpendicularly to the skin, which is examined 4 hours later. By varying the duration of application and pressure, a quantitative assessment of the severity of delayed pressure urticaria can be made.[3]

The cause of delayed pressure urticaria is unknown. The prolonged time course of the wheals distinguishes them from other categories of chronic urticaria and there is no vasculitis histologically. Our studies revealed elevated tissue levels of IL-6 but not arachidonate metabolites in lesional skin[8,9] and close similarities to late-phase reactions has been noted.[7]

The practical importance of establishing the diagnosis is evident. Apart from the predictably poor response to antihistamines and the poor prognosis (delayed pressure urticaria pursues a very long-term course), there are important management implications. If delayed pressure urticaria turns out to be an important component of the symptoms of a patient with CIU, there is little point in further autoimmune laboratory workup because delayed pressure urticaria is independent of the patient's autoantibody status (see below), and establishing an autoimmune basis for the patient's CIU is of no assistance at all in the management of the delayed pressure urticaria. Large doses of systemic steroids may be needed to control this physical urticaria in severely afflicted patients.

COLD URTICARIA

There are a number of rare subtypes of cold urticaria, but for the purposes of this account only 2 subtypes need to be considered: primary acquired cold urticaria ("essential" cold urticaria) and secondary acquired cold urticaria. Compared with most other physical urticarias, these have been intensively studied.

Primary acquired ("essential") cold urticaria

Primary acquired cold urticaria is a physical urticaria of children and young adults. Characteristically, local whealing and itching occur within a few minutes of applying a solid or fluid cold stimulus to the skin. The wheal persists for about a half hour or less before fading without a residual trace. This physical urticaria may also occur in the oropharynx (eg, after a cold drink), which may present as urticaria or angioedema. Systemic symptoms, occasionally severe and anaphylactoid, may occur after extensive exposure such as immersion in cold water.

There may be a recent history of an intercurrent virus infection *(Mycoplasma pneumoniae)*[10] and passive transfer has been successfully demonstrated to recipient human[11] and nonhuman primate[12] skin, indicating the role of a serum factor, possibly IgM or IgE.[13] Heterozygous deficiency of the protease inhibitor α_1-antichymotrypsin has been demonstrated and may be etiologically important in some patients.[14]

The dermal mast cell population density is within normal limits and there is normally no evidence of vasculitis.[15] However, repeated cold challenge at the same site can evoke evidence of structural dermal postcapillary venular damage, raising the possibility of involvement of circulating immunoreactants.[16] We and others have studied the pharmacologic mediators involved in cold urticaria by a variety of methods, including examination of venous effluent recovered from the antecubital vein of the cold-challenged forearm. Histamine has been consistently recovered, although it is probably not by itself accountable for the whealing,[15] and other mediators are implicated as well.[17-19] Exactly how dermal mast cells are triggered to release histamine and other mediators is unclear, although interesting studies by Gruber et al[20] raise the possibility of an autoimmune (possibly anti-IgE) mechanism. The prognosis is good, with spontaneous improvement occurring in an average of 2 to 3 years. Diagnosis is usually made by applying an ice cube for 5 to 15 minutes to skin and, after allowing an interval for skin rewarming, observing development of whealing.

Secondary acquired cold urticaria

The diagnosis of secondary acquired cold urticaria depends on being able to demonstrate a cryoglobulin, cold agglutinin, or possibly cryofibrinogens in a patient with cold urticaria. This finding occurs in about 5% of patients with cold urticaria. The prognosis is that of the underlying disorder.

Demonstration of a cryoglobulin should prompt a search for an underlying cause, including chronic hepatitis B or C infection, lymphoreticular malignancy, or glandular fever. These considerations have been reviewed by Wanderer.[21]

The clinical picture differs from that of the "essential" type. Wheals are more persistent, may manifest purpura, and demonstrate the histologic features of vasculitis on skin biopsy specimens. The cryoglobulins may be polyclonal (post infection) or monoclonal (IgG or IgM) and complement activation may be involved.[22] A positive serologic test for syphilis has been described in cold urticaria, associated with a circulating hemolysin.[23]

CHOLINERGIC URTICARIA

In its milder presentations, cholinergic urticaria is probably the most common of all the physical urticarias. Often referred to trivially as "heat bumps," it probably occurs at some time during the lives of at least 15% of the population. It has been the subject of several useful reviews.[24,25]

Cholinergic urticaria is a physical urticaria predominantly in teenagers and younger adults and carries a good prognosis for eventual improvement, although I have had patients in whom troublesome symptoms have persisted into middle age. At least 50% of patients are also atopic. Characteristically itchy, small, red macules or papules occur on the neck, trunk, forearms, wrists, and thighs in response to heat (environmental or a hot bath or shower), exercise, or emotional stress. All these stimuli cause eccrine sweating, but the latter is not necessary as such because the rash has been described in patients with anhidrosis.[26] However, it is likely that activation of the cholinergic sympathetic innervation of sweat glands is a key mechanism. The rash can be blocked by prior atropinization of the skin.[27] The rash usually subsides within minutes if the patient "chills off." However, occasional patients in whom the rash is continuous and persistent are well recognized and represent a diagnostic trap for the unaware.[28] Severely affected patients may get associated angioedema of the skin or mucous membranes.[29] Wheezing associated with attacks of cholinergic urticaria are not uncommon even in milder cases; in more severe attacks syncope has been known to occur.[29] Cholinergic urticaria can occur without visible skin lesions (cholinergic pruritus).

The cause is unknown. A recent suggestion that some form of sweat allergy is involved[30] has not been confirmed. That a transferable serum factor may be implicated has been supported by successful transfer using serum to nonhuman primates in some cases.[31]

A small subset of patients with cholinergic urticaria will have the rash only as a consequence of food ingestion followed by exercise.[32] Some of these patients appear to have IgE-mediated allergy to certain specific food items, whereas in others the triggering factor appears to be nonspecifically related to food ingestion. The diagnosis is confirmed by exercise or hot bath challenge testing. This subject has been reviewed.[24]

We have also demonstrated reduced plasma levels of certain protease inhibitors in cholinergic urticaria.[33] That this finding is clinically significant is suggested by a placebo-controlled double-blind study that has demonstrated the ability of oral anabolic steroid treatment to both correct these lowered protease inhibitor levels and, in parallel, cause amelioration of the rash.[34] However, the routine treatment remains the use of a low-sedation H_1 antihistamine with or without an anxiolytic such as oral propranolol. Severely affected unresponsive patients may be treated cautiously with an anabolic steroid such as stanazolol. This unlicensed treatment, which is less satisfactory in women owing to the possibility of causing mild virilization, should be monitored by regular liver function tests and liver scans.

CHRONIC IDIOPATHIC URTICARIA

Clinical features

Conventionally, CIU is defined as the daily, or almost daily, occurrence of urticarial wheals for at least 6 weeks. Intermittent urticaria, although a common entity, is less well recognized. It consists of bouts of urticaria lasting days or weeks with intervals of days, weeks, or months in between. It will be considered jointly with classic CIU for the purposes of this discussion. Angioedema occurs concurrently with CIU in about 50% of cases[1] and delayed pressure urticaria in about 40%.[7]

As already discussed, care must be taken to exclude physical urticaria as the sole, or predominant, cause of the patient's disability, especially because physical urticarias frequently occur concurrently with CIU. UV is also a very important differential diagnosis (see below). CIU is common, occurring in 0.1% of the population, and 20% still have the disease after 20 years has elapsed. There is no increased frequency of atopy in CIU and the clinical features of the urticaria and angioedema are as described above (p 664). However, in comparison with physical urticarias, the individual urticarial wheals last longer—at least 8 to 12 hours. Unlike UV wheals, wheals of CIU do not cause residual pigmentation. Systemic symptoms are minimal. Patients frequently feel fatigued, especially during relapses, but respiratory, gastrointestinal, and arthralgic symptoms are rare. Angioedema may affect the oropharynx but is not life threatening. Its etiology is assumed to be the same as that for the urticaria. Gastrointestinal symptoms may occasionally accompany severe attacks. Pruritus is nearly always severe and especially troublesome in the evening and nighttime.[1]

CIU and angioedema are rare in childhood; the average duration of the disease is about 3 to 5 years in

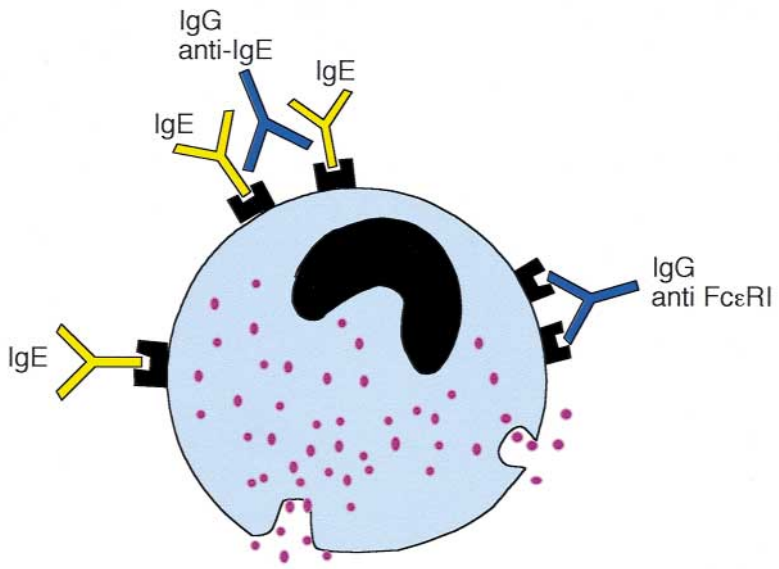

FIG 2. Functional autoantibodies of CIU. IgG–anti-IgE antibodies combine with and cross-link adjacent receptor-bound IgE. IgG–anti-FcεRI antibodies combine with and crosslink adjacent α-chains of FcεRI. Black notched membrane structures represent α-chain of FcεRI expressed on the surface of a dermal mast cell.

adults.[2] It is a cause of serious personal, social, economic, and occupational disability comparable with that associated with severe coronary heart disease.[35] Its clinical, pathologic, and etiologic features have recently been reviewed.[36]

ETIOLOGY

The target cell for CIU and angioedema is the dermal mast cell, and any hypothetic etiological mechanism should explain how this cell becomes repeatedly and extensively activated, leading to release of histamine and other mediators. No doubt other cell types are also involved, including the basophil.[37] Until recently there has been a paucity of convincing evidence-based causes. Chronic infection has frequently been cited—most recently *Helicobacter pylori.* However, recent reports have failed to confirm this association.[38,39] I have yet to see a patient in whom parasite infestation proved causative, but in regions where infestation with high loads of parasites occur, an association is possible and this needs further study. Most patients have at some time believed that food "allergy" is causative. Certainly IgE-mediated type I allergy (Gell and Coombs) caused by foods is an important cause of acute urticaria but can rarely, if ever, be substantiated as a cause of CIU. Idiosyncratic reactions to food additives are alleged to be important causes by a number of authors. However, at least in my own practice, food additives can be substantiated to be causative in no more than 5%. The gold standard must be positive placebo-controlled challenge testing.[40-42] Exclusion diets, favored by some authors, are extremely difficult to carry out satisfactorily owing to the prolonged duration of this procedure, poor patient compliance, and, invariably, ambiguous results. Aspirin does exacerbate chronic urticaria nonspecifically, as do intercurrent virus infections. However, neither are causative. Thus, until recently, the cause in the majority of patients with CIU remained enigmatic.

As early as 1962 it was reported that the absolute blood basophil count in unselected patients with CIU was significantly lower than in otherwise comparable nonurticarial controls.[43] Subsequently in 1974 I reported[44] that the basophils of unselected CIU patients released less histamine when challenged in vitro by a range of concentrations of anti-IgE than did basophils of matched nonurticarial controls. However, release evoked by nonimmunologic stimuli, which did not depend on IgE or the high-affinity IgE receptor (FcεRI), including compound 48/80, did not differ significantly between the 2 groups. These findings suggested the presence of a circulating factor causing desensitization via IgE.

In 1986 Grattan et al[45] reported the presence of a serum factor that caused whealing on autologous intradermal injection in some but not all patients with CIU. However, it was not until 1993[46] that my laboratory confirmed the identity of this factor as an IgG with specificity for the α-chain of the high-affinity IgE receptor (FcεRIα). Subsequent studies[47] demonstrated this autoantibody as a causative factor in about 25% of patients with CIU. A further 5% of patients proved to have functional anti-IgE autoantibodies[47] (Fig 2). That a subset of patients with CIU had an autoimmune basis as a result of anti-FcεRIα autoantibodies was subsequently confirmed by several authors,[48-50] the frequency ranging from 25% to 45% of the total patients with CIU. The IgG subtypes proved to be predominantly IgG1 and IgG3.[51]

That CIU is, at least in some patients, autoimmune is not too surprising. An increased frequency of thyroid autoimmune disease in CIU has previously been reported by ourselves[52] and others.[53] In accordance with the proposed autoimmune basis of this subset of patients with chronic urticaria, we have also demonstrated its positive association with certain HLA-DR and -DQ alleles that are characteristically known to show increased frequency in autoimmune diseases.[54] Our own data suggest that normally IgG anti-FcεRIα autoantibodies cause direct cross-linking of adjacent receptors, thus triggering mast cell or basophil activation. However, recent work[55] raises the possibility that monovalent combination may take place, involving complement activation. This probably only occurs in instances where there is a low population density of FcεRI on the basophil or dermal mast cell membrane. The reason why little or no activation of mast cells occurs at other organ and tissue sites occurs is not clear. In vitro, lung and other noncutaneous mast cells release histamine in response to anti-FcεRIα autoantibodies.[47] However, lung mast cells are unresponsive to activated complement. Possibly, differences in interstitial fluid levels of IgG between skin and lung may also play a part.

Immunoreactive non-histamine-releasing anti-FcεRI autoantibodies have been detected in other nonurticarial autoimmune diseases, including dermatomyositis, pemphigus, and pemphigoid.[51] However, up to the present only chronic urticaria patients have been shown to manifest functional histamine-releasing anti-FcεRI autoantibodies. They do not occur in physical urticarias, atopic eczema, or other diseases in which activated mast cells have been implicated.

Of course, other circulatory factors may well also be involved, including the IgE-dependent histamine-releasing cytokine and other histamine-releasing cytokines reported by different North American groups.[56,57]

Diagnosis

Patients with autoimmune (anti-FcεRIα or anti-IgE) autoantibodies have no distinctive diagnostic clinical features. They do tend to have more severe urticaria[1] and histologic examination shows pronounced eosinophil degranulation in older lesions compared with nonautoimmune cases, but these differences are not sufficiently distinctive to use diagnostically.[58] There is no vasculitis, and direct immunofluorescence yields no specific findings. However, re-examination of the blood basophil count has revealed an extreme paucity of these cells in the peripheral blood of autoimmune compared with nonautoimmune cases, which could form the basis of a screening test.[37] Serum IgE levels are not significantly different from those of nonautoimmune patients.[1] Currently the clinical diagnosis depends on autologous serum skin testing. Maximum specificity and sensitivity is obtained if serum or plasma, obtained by venisection during a phase of disease activity, is injected, in a volume of 0.05 mL intradermally, into clinically uninvolved skin. The reaction at the injected site is examined 30 minutes later. A wheal with a diameter at least 1.5 mm greater than a control saline solution wheal is deemed positive[59] (Fig 3).

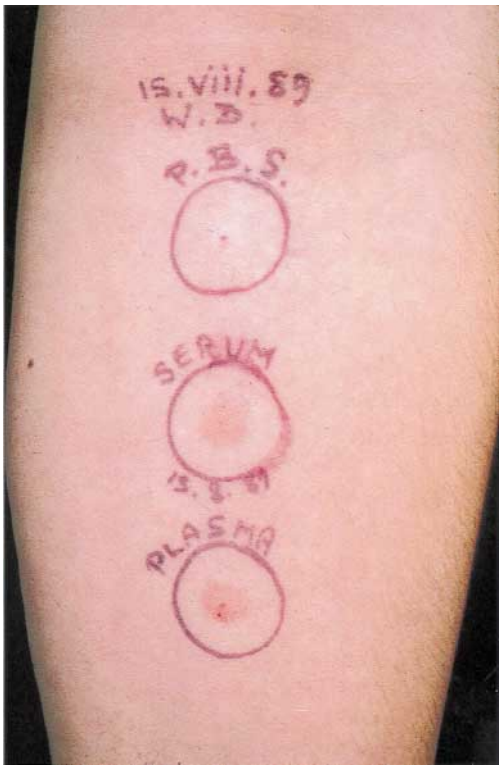

FIG 3. Autologous serum-plasma skin test. *PBS,* Saline solution negative control; serum and plasma are injected in a volume of 0.05 mL and the reaction read at 30 minutes. Both serum and plasma have given positive responses.

A positive test is suggestive but not diagnostic of an autoimmune basis for the patient's chronic urticaria. Confirmation is needed by in vitro testing of the patient's serum for anti-FcεRIα or anti-IgE autoantibodies. Regrettably, despite attempts by our own and other laboratories, no satisfactory ELISA has been developed. We rely on demonstration of histamine release from basophils of healthy low- and high-IgE donors,[47] and this remains the gold standard. However, it is time consuming and inconvenient. Western blotting is also widely used and we have shown a good concordance between results with Western blotting and with basophil histamine release using the same sera (Maurer et al, unpublished data). However, as previously indicated, false-positive results may occur in sera of patients with nonurticarial autoimmune disease because of the presence of non-histamine-releasing anti-FcεRIα immunoreactivity.

In summary, identification of disease-specific anti-FcεRIα histamine-releasing autoantibodies in 25% to 45% of CIU is clearly a useful step forward, but what about the other 50%? A few of these (no more than 5%) may have demonstrable food additive reactivity as confirmed by challenge testing (see above). Indirect evidence suggests that many of the remainder may also be autoimmune. Autoimmune and nonautoimmune cases are indistinguishable clinically and histologically. The peripheral blood basophil numbers, although almost unmeasurable in autoimmune cases, are also lower than

values in healthy controls in nonautoimmune patients. Finally, the autologous serum skin test is frequently positive although in vitro testing for histamine release from low- and high-IgE basophils turns out to be negative. Regrettably, sensitivity has had to be sacrificed in the interests of high specificity in the in vitro test.

Treatment of CIU

The routine management of autoimmune and nonautoimmune chronic urticaria is the same. General measures including avoidance of alcohol overuse, overtiredness, and overheated surroundings are important. It is also important to reassure anxious patients that the eruption is not a hallmark of cancer, HIV infection, or other underlying disease. On the other hand, elaborate and unnecessary dietary restrictions should be discouraged. Frequent tepid showers and "as-required" application of 1% menthol in aqueous cream are useful measures during relapses and well appreciated by patients.

All patients with frequent outbreaks of wheals and itching should be offered H_1 antihistamine treatment. It is important to impress on patients that regular daily dosage is essential if maximum benefit is to be achieved. Results after as-required dosage are almost always inferior and often account for alleged treatment failures. It is my practice to offer an average adult a single morning dose of a low-sedation H_1 antihistamine such as loratidine 10 mg, cetirizine 10 mg, or fexofenadine 180 mg. Cetirizine is mildly sedative. Sedation occurs with doses of loratidine above 10 mg, but I prescribe 360 mg of fexofenadine (this is twice the licensed dose) to more severely pruritic patients without risk of sedation because this antihistamine is lipophobic and does not penetrate the blood-brain barrier. However, it is important to take into account the diurnal periodicity of symptoms in each patient. There is no point in prescribing a morning dosage of an antihistamine if symptoms are restricted to evening and nighttime, as is frequently the case.[1]

In the event that pruritus at night is troublesome, I add a sedative antihistamine such as hydroxyzine 25 to 50 mg. In more severely afflicted patients the tricyclic antihistamine doxepin 25 to 50 mg is useful as a single nocturnal dose. Because anxiety and depression are a feature of patients with severe chronic urticaria and angioedema, this drug, which is also an H_2 antihistamine, a powerful sedative, an anxiolytic, and an antidepressant, is appropriate. However, doxepin is metabolized by the cytochrome P450 enzyme system and care should be taken to avoid concurrent administration of other drugs (eg, macrolide antibiotics) similarly metabolized. It is also important to warn patients who may require, for example, motor car driving skills in the morning that their cognitive function and reflex activity may be impaired for up to 24 hours after a nocturnal dose of hydroxyzine, doxepin, or similar sedative H_1 antihistamine. The role of H_2 antihistamines is controversial. We have shown in several controlled studies[6,60,61] that there is a statistically significant benefit from combination treatment with H_1 and H_2 antihistamines, but it is unclear whether this represents a significant clinical benefit. I tend to give patients the benefit of the doubt on this issue, especially if the patient happens to be troubled by gastric hyperacidity, heartburn, or dyspepsia.

The role of systemic corticosteroids is limited. I occasionally prescribe short tapering courses (eg, 30 mg of prednisolone daily reducing to zero over 10 days) in special circumstances where, for example, rapid control is needed to cover an important social or occupational event such as a wedding ceremony or an important examination. However, prolonged daily treatment nearly always leads to severe systemic toxicity accompanied by poor control of urticaria and severe rebound on attempts to withdraw.

Leukotriene antagonists have received some attention as potential nonsteroid therapies for chronic urticaria, but their role, if any, remains to be established.

What can be done for the severely affected patient recalcitrant to the above measures? If the patient turns out to be autoantibody positive, there are a number of options (see below). Autoantibody-negative patients can be considered for cyclosporine treatment. Cyclosporine is of proved value in autoantibody-positive chronic urticaria[62] but is also effective in most cases of severe autoantibody-negative disease. I use doses of 3 to 4.5 mg/kg for up to 3 months at a time. Most (>75%) show an excellent response. Of these, one third remain in remission after withdrawal, one third relapse but only mildly, and one third relapse to the extent that they were affected before cyclosporine treatment. I have only once seen what appeared to be a "rebound" relapse on withdrawal. Obviously blood pressure and renal function need to be monitored and the treatment is unsuitable for patients with risk factors related to malignant disease such as a strong family or personal history of cancer, positive cervical smear, etc.

Management of autoimmune urticaria

As previously indicated, the initial treatment is the same regardless of whether the patient has an autoimmune etiology for the disease. However, patients with autoimmune chronic urticaria tend to be more severely affected[35] and on the whole less responsive to H_1 antihistamine treatment. In these circumstances, and where the disease is clearly causing severe impairment of the patient's social, occupational, and domestic life, a number of options can be considered. Cyclosporine has already been mentioned. We have recently completed a placebo-controlled trial of oral cyclosporine in autoantibody-positive patients with chronic urticaria,[62] with impressive results. The details of the regimen for cyclosporine treatment are as for nonautoimmune patients (see above). Other options include intravenous Ig infusions[63] and plasmapheresis.[64] The reader is referred to the appropriate references for further details. However, it should be emphasized that none of these measures are curative and that they are most appropriately carried out in a specialized center.

REFERENCES

1. Sabroe RA, Seed PT, Francis DM, Barr RM, Black AK, Greaves MW. Chronic idiopathic urticaria: comparison of the clinical features of patients with and without anti-FcεRI or anti-IgE autoantibodies. J Am Acad Dermatol 1999;40:443-50.
2. Champion RH, Roberts SOB, Carpenter RG, Roger JH. Urticaria and angioedema—a review of 554 patients. Br J Dermatol 1969;81:588-97.
3. Black AK, Lawlor F, Greaves MW. Consensus meeting on the definition of physical urticarias and urticarial vasculitis. Clin Exp Dermatol 1996;21:424-6.
4. Murphy GM, Zollman PE, Greaves MW, Winkelmann RK. Symptomatic dermographism (factitious urticaria)—passive transfer experiments from human to monkey. Br J Dermatol 1987;116:801-4.
5. Greaves MW, Sondegaard J. Urticaria pigmentosa and factitious urticaria: direct evidence for release of histamine and other smooth-muscle-contracting agents in dermographic skin. Arch Dermatol 1970;101:418-25.
6. Breathnach SM, Allen R, Milford-Ward A, Greaves MW. Symptomatic dermographism: natural history, clinical features and response to therapy. Clin Exp Dermatol 1983;8:463-76.
7. Barlow RJ, Warburton F, Watson K, Black AK, Greaves MW. The diagnosis and incidence of delayed pressure urticaria in patients with chronic urticaria. J Am Acad Dermatol 1993;24:954-8.
8. Lawlor F, Bird C, Camp RDR, Barlow R, Barr RM, Black AK, et al. Increased interleukin-6 but reduced interleukin-1 in delayed pressure urticaria. Br J Bermatol 1993;128:500-3.
9. Lawlor F, Barr RM, Black AK, Cromwell I, Isaacs J, Greaves MW. Arachidonic acid transformation is not stimulated in delayed pressure urticaria. Br J Dermatol 1989;121:317-21.
10. Neittaanmaki JJ. Cold urticaria: clinical findings in 270 patients. J Am Acad Dermatol 1985;13:636-44.
11. Houser DD, Arbesman CE, Ito K, Wicher K. Cold urticaria: immunological studies. Am J Med 1970;49:23-33.
12. Misch K, Black AK, Greaves MW, Almosawi T, Stanworth DR. Passive transfer of idopathic cold urticaria to monkeys. Acta Derm (Stockh) 1983;63:163-4.
13. Wanderer AA, Maselli R, Ellis EF, Ishizaka KJ. Immunological characterisation of serum factors responsible for cold urticaria. Allergy 1971;48:13-22.
14. Wallengren LB. Heterozygous a1-antichymotrypsin deficiency may be associated with cold urticaria. Allergy 1992;47:456-8.
15. Lawlor F, Black AK, Breathnach AS, McKee P, Sarath Chandra P, Bhogal B, et al. A timed study of the histopathology, direct immunofluorescence and ultrastructural findings in idiopathic cold contact urticaria over a 24 hour period. Clin Exp Dematol 1989;14:416-20.
16. Eady RAJ, Greaves MW. Induction of cutaneous vasculitis by repeated cold challenge in cold urticaria. Lancet 1978;1:336-7.
17. Soter NA, Wasserman SI, Austen KF. Cold urticaria: release into the circulation of histamine and eosinophil chemotactic factor of anaphylaxis during cold challenge. N Engl J Med 1976;294:687-90.
18. Keahey TM, Greaves MW. Cold urticaria: dissociation of cold-evoked histamine release and urticaria following cold challenge. Arch Dermatol 1980;116:174-7.
19. Ormerod AD, Black AK, Dawes J, Murdock RD, Koro O, Barr RM, Greaves MW. Prostaglandin D2 and histamine release unaccompanied by evidence of platelet activation. J Allergy Clin Immunol 1988;82:586-9.
20. Gruber BC, Thaeza MC, Marchase MJ, Aquello V, Kaplan AP. Autoantibodies in urticarial syndromes. J Invest Dermatol 1988;90:213-7.
21. Wanderer AA. Cold urticaria syndromes: historical background, diagnostic classification, clinical and laboratory characteristics, pathogenesis and management. J Allergy Clin Immunol 1990;85:965-81.
22. Constanzi JJ, Coltman JR, Donaldson VH. Activation of complement by a monoclonal cryoglobulin associated with cold urticaria. J Lab Clin Med 1969;74:902-10.
23. Harris KE, Lewis T, Vaughan JM. Haemoglobinuria and urticaria from cold occuring singly or in combinations: observations referring especially to the mechanism of urticaria with some remarks upon Raynaud's disease. Heart 1929;14:305-36.
24. Hirschmann JV, Lawlor F, English SJC, Lowback JB, Winkelmann RK, Greaves MW. Cholinergic urticaria. Arch Dermatol 1987;123:462-7.
25. Zuberbier T, Althaus C, Chantraine-Hess H, Czarnetski BM. Prevalence of cholinegic urticaria in young adults. J Am Acad Dermatol 1994;31:478-81.
26. Kay DM, Maibach HR. Pruritus and acquired anhidrosis: two unusual cases. Arch Dermatol 1969;100:291-3.
27. Herxheimer A. The nervous pathway mediating cholinergic urticaria. Clin Sci 1956;15:195-205.
28. Murphy GM, Black AK, Greaves MW. Persisting cholinergic erythema—a variant of cholinergic urticaria. Br J Dermatol 1983;109:343-8.
29. Lawrence CM, Jorizzo JL, Black AK, Coutts A, Greaves MW. Cholinergic urticaria with associated angioedema. Br J Dermatol 1981;105:543-50.
30. Adachi J, Aoki T, Yamatodari A. Demonstration of sweat allergy in cholinergic urticaria. J Dermatol Sci 1994;7:142-9.
31. Murphy GM, Greaves MW, Zollman P, Stanworth D. Cholinergic urticaria: passive transfer experiments from human to monkey. Dermatologica 1988;177:338-40.
32. Kivity S, Snech E, Grief J, Topilsky N, Mekori YA. The effect of food and exercise on the skin response to compound 48/80 in patients with food-associated, exercise-induced urticaria angioedema. J Allergy Clin Immunol 1988;81:1155-8.
33. Eftekhari N, Milford Ward A, Allen R, Greaves MW. Protease inhibitor profiles in urticaria and angioedema. Br J Dermatol 1980;103:33-9.
34. Wong E, Eftekhari N, Greaves MW, Milford Ward A. Beneficial effects of danazol on symptoms and laboratory changes of cholinergic urticaria. Br J Dermatol 1987;116:553-6.
35. O'Donnell BF, Lawlor F, Simpson J, Morgan M, Greaves MW. The impact of chronic urticaria on quality of life. Br J Dermatol 1997;136:197-201.
36. Greaves MW. Chronic urticaria. N Engl J Med 1995;332:1767-72.
37. Sabroe RA, Francis DM, Barr RM, Black AK, Greaves MW. Anti-FceRI autoantibodies and basophil histamine releasability in chronic idiopathic urticaria. J Allergy Clin Immunol 1998;102:651-8.
38. Schnyder B, Helbling A, Pichler WJ. Chronic idiopathic urticaria: natural course and association with Heliobacter pylori infection. Int Arch Allergy Immunol 1999;119:60-83.
39. Liutu M, Kalimo K, Uksila J, Kalimo H. Etiological aspects of chronic urticaria. Int J Dermatol 1998;37:515-9.
40. May CD. Are confusion and controversy about food hypersensitivity really necessary? J Allergy Clin Immunol 1985;75:329-33.
41. Pastorello EA. Evaluating new tests for the diagnosis of food allergy. Allergy 1995;50:289-91.
42. Doeglas HMG. Reactions to aspirin and food additives in patients with chronic urticaria including the physical urticarias. Br J Dermatol 1975;93:135-144.
43. Rorsman H. Basopenia in urticaria. Acta Allergol 1962;17:168-84.
44. Greaves MW, Plummer VM, McLaughlan P, Stanworth DR. Serum and cell-bound IgE in chronic urticaria. Clin Allergy 1974;4:265-71.
45. Grattan CEH, Wallington TB, Warin RP. A serological mediator in chronic idiopathic urticaria: a clinical immunological and histological evaluation. Br J Dermatol 1986;114:583-90.
46. Hide M, Francis DM, Grattan CEH, Greaves MW. Autoantibodies against the high affinity IgE receptor as a cause for histamine release in chronic urticaria. N Engl J Med 1993;328:1599-604.
47. Niimi N, Francis DM, Kermani F, Greaves MW, Black AK, O'Donnell BF, et al. Dermal mast cell activation by autoantibodies against the high affinity IgE receptor in chronic urticaria. J Invest Dermatol 1996;106:1001-6.
48. Fiebiger E, Maurer D, Holub H, Reininger B, Hartmann G, Woisetschlager M, et al. Serum IgG autoantibodies directed against the a-chain of FceRI: a selective marker and pathogenetic factor for a distinct subset of chronic urticaria and pathogenetic factor for a distinct subset of chronic urticaria patients? J Clin Invest 1995;96:2606-12.
49. Zweiman B, Valenzano M, Atkins PC, Tanus T, Getsy JA. Characteristics of histamine-releasing activity in the sera of patients with chronic idiopathic urticaria. J Allergy Clin Immunol 1996;98:89-98.
50. Tong LJ, Balakrishnan G, Kochan JP, Kinet J-P, Kaplan AP. Assessment of autoimmunity in patients with chronic urticaria. J Allergy Clin Immunol 1997;99:461-5.
51. Fiebiger E, Hammerschmid F, Stingl G, Maurer D. Anti-FceRI autoantibodies in autoimmune-mediated disorder: identification of a structure-function relationship. J Clin Invest 1998;101:243-51.
52. O'Donnell BF, Black AK, Greaves MW. Organ- and non-organ-specific autoimmunity in chronic urticaria [abstract] Br J Dermatol 1995;133(145 Suppl):42.
53. Leznoff A, Sussman GL. Syndrome of idiopathic chronic urticaria and angioedema with thyroid autoimmunity—a study of 90 patients. J Allergy Clin Immunol 1989;84:66-71.

54. O'Donnell BF, O'Neill CM, Francis DM, Niimi N, Barr RM, Barlow RJ, et al. Human leucocyte antigen class II associations in chronic idiopathic urticaria. Br J Dermatol 1999;140:853-8.
55. Ferrer M, Nazakawa K, Kaplan AP. Complement dependence of histamine release in chronic urticaria. J Allergy Clin Immunol 1999;104:169-72.
56. Claveau J, Lavoie A, Brunet C, Bedford PM, Hiber J. Chronic idiopathic urticaria: possible contribution of histamine releasing factor to the pathogenesis. J Allergy Clin Immunol 1993;92:132-7.
57. MacDonald SM, Rafnar T, Langdon J, Lichtenstein LM. Molecular identification of an IgE-dependent histamine releasing factor. Science 1995;269:688-90.
58. Sabroe RA, Poon E, Orchard GE, Lane D, Francis DM, Barr RM, et al. Cutaneous inflammatory cell infiltrate in chronic idiopathic urticaria: comparison of patients with and without anti-FceRIa or anti-IgE autoantibodies. J Allergy Clin Immunol 1999;103:484-93.
59. Sabroe RA, Grattan CEH, Francis DM, Barr RM, Black AK, Greaves MW. The autologous serum sin test: a screening test for autoantibodies in chronic idiopathic urticaria. Br J Dermatol 1999;140:446-52.
60. Commens CA, Greaves MW. Cimitidine in chronic idiopathicurticaria: a randomised double-blind study. Br J Dermatol 1978;99:675-6.
61. Thomas SE, Glenny H, Bleehen SS, Grewel MW, Pilgrim J, Rowell N, et al. Cimetidine and chlorpheniramine in the treatment of chronic idiopathic urticaria: a multi-centre randomised double-blind study. Br J Dermatol 1987;117:81-8.
62. Grattan CEH, O'Donnell BF, Francis DM, Niimi N, Barlow RJ, Seed PT, et al. Randomised double-blind study of cyclosporin in chronic idiopathic urticaria. Br J Dermatol 1999. In press.
63. Grattan CEH, Francis DM, Slater NGP, Barlow RJ, Greaves MW. Plasmapheresis for severe unremitting chronic urticaria. Lancet 1992;339:1078-80.
64. O'Donnell BF, Barr RM, Blac AK, Francis DM, Greaves MW. Intravenous immunoglobulin in chronic autoimmune urticaria. Br J Dermatol 1998;138:101-6.