

Pathophysiology of Chronic Urticaria

Malcolm W. Greaves

Hospital Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia, and St. Johns' Institute of Dermatology, St. Thomas' Hospital, London, UK

Key Words

Urticaria · Autoimmunity · Mast cell · *Helicobacter pylori* · Immunotherapy

Abstract

Chronic urticaria includes several different subsets with distinct pathophysiologies, and with important implications for investigation and treatment. Chronic 'idiopathic' urticaria represents a special challenge, which, until recently, was not taken up by dermatological or immunological investigators. However, it has now emerged that at least 30% of patients possess histamine-releasing autoantibodies against FcεR1, or less commonly IgE itself. These autoantibodies are causative. Recent work implicates complement activation in most cases. Functional (i.e. histamine releasing) autoantibodies are specific to chronic urticaria. However, immunoreactive (non-histamine-releasing) anti-FcεR1 autoantibodies can be found in sera of patients with physical urticarias and with autoimmune connective tissue and bullous diseases. The reason for the occurrence of this disease type in some individuals but not others is unclear. One possibility is the development, in genetically predisposed persons, of autoantibodies by molecular mimicry – perhaps against lipopolysaccharide of *Helicobacter pylori*, an organism frequently infecting the upper gastrointestinal tract of chronic urticaria patients.

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Introduction

Hippocrates described urticaria in the fifth century BC as a response of skin to contact with stinging nettles. However, the use of the term 'urticaria' to describe this common dermatosis does not emerge until the late 17th century, and at about this time its regular association with angioedema was also recognized. Important milestones in understanding of the pathogenesis of the wheals and itch associated with the condition include the discovery of the mast cell by Ehrlich at the beginning of the 20th century, the finding by Dale of histamine a little later and, in the 1920s, the characterization by Lewis of the vascular responses of human skin to histamine. In the 1940s the studies of Riley and West demonstrated that the principal source of histamine in the skin is the dermal mast cell. Finally, Kaplan et al. [1] were able to obtain direct evidence of release of histamine in lesional skin of chronic idiopathic urticaria. These historical landmark events were recently reviewed [2].

What Is Chronic Urticaria?

When the individual lesions of an inflammatory rash last less than 24 h, then the patient has, by generally accepted definition, got urticaria. There are exceptions to the 24-hour rule. Wheals of both urticarial vasculitis and delayed pressure urticaria last longer than 24 h. Additionally, almost invariable features include pruritus and the lack of pigmentation, scarring or any other visible sign (except, rarely, scratch marks) in skin recently involved in urticaria.

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Correspondence to: Prof. Malcolm W. Greaves
Damasara Heights
56 Jalan Jelutong
Kuala Lumpur 50490 (Malaysia)
Fax +60 603 254 2393

Table 1. Subsets of chronic urticaria [5]

Subtype	Frequency, %
Chronic idiopathic urticaria	48
Physical urticarias ¹	40
Urticarial vasculitis	6
Food additive-evoked urticaria ²	6

¹ See table 2.² Confirmed by placebo-controlled challenge testing.**Table 2.** Subsets of physical urticarias¹ [6]

Cholinergic urticaria
Symptomatic dermatographism
Delayed pressure urticaria
Cold urticaria
Solar urticaria
Aquagenic urticaria ²
Heat urticaria ²
Vibratory angioedema ²

¹ Listed in rank order of frequency.² Not discussed further in this account.

By tacit agreement of most investigators, authors and clinicians, urticaria becomes designated as ‘chronic’ when wheals have occurred daily or almost daily for at least 6 weeks. Angioedema occurs concurrently with chronic urticaria in 90% of patients [3] and, for the purposes of discussing pathophysiology, chronic urticaria and angioedema can be considered jointly. The only significant difference between the two is the level of involvement in the skin. The vascular changes are predominantly dermal in urticaria, and deep dermal and subcutaneous or submucosal in angioedema. Unlike angioedema, urticaria rarely affects mucous membranes.

Subtypes of Chronic Urticaria

Chronic urticaria is not a single disease [4]. Physical urticarias show both clinical similarities and differences, compared to ‘ordinary’ chronic urticaria. Likewise, urticarial vasculitis manifests striking differences compared to other forms of urticaria. There is also a small subgroup of patients with challenge test-confirmed food additive-evoked urticaria. At least 50% of patients with chronic urticaria have chronic ‘idiopathic’ urticaria (CIU). These

subtypes (table 1) will be discussed individually as, although outwardly presenting with similar urticarial features, their pathophysiology is different.

Physical Urticarias

These are chronic urticarias provoked by a physical stimulus, usually applied directly to the skin or mucosal surface, and eliciting a wheal-and-flare or angioedematous response, with or without pruritus, locally at the site of application. The important members of this group are listed in approximate order of frequency in table 2. The criteria for diagnosis have been recently published [6].

Cholinergic Urticaria

Cholinergic urticaria occurs in up to 20% of people and is often almost unnoticed in its milder forms. Typically patients complain of pruritus in association with exertion, emotional stress, heat (e.g. hot shower) and hot food or drinks. However, in the straightforward common form of cholinergic urticaria, no food allergy is involved. A visible fine macular or papular urticarial eruption is nearly always present but may be overlooked by the patient, especially if the skin is heavily pigmented. In moderately or severely affected patients, a symmetrical erythematous monomorphic maculopapular eruption is clearly visible, typically on the forearms, wrists, neck and axillae but also frequently generalized. Individual wheals, which are often surrounded by both a flare and an outer halo of pallor, may become confluent, causing large areas of oedema in severely affected patients. Characteristically, the rash is transient, rarely lasting more than 30 min if the patient chills off. It shows a strong positive association with atopy. For a detailed account of diagnosis, the reader is referred to Commens and Greaves [7].

The development of the rash of cholinergic urticaria is intimately associated with eccrine sweating, but is not dependent on it since cholinergic urticaria can occur in anhidrotic individuals. Herxheimer [8] clearly demonstrated the importance of an intact sympathetic cholinergic pathway in development of whealing, the rash being easily blocked by prior atropinisation of the skin. A recent suggestion that allergy to sweat could be causative [9] has yet to be confirmed, and could not be supported by the author’s own (unpublished) observations. Passive transfer experiments suggest that a circulating serum factor may be involved [10]. We [11] have also demonstrated the association of cholinergic urticaria with lowered levels of plasma protease inhibitors, and this has led to successful

use of the attenuated androgen stanazolol as systemic therapy in severely affected patients, as demonstrated by placebo-controlled trials [12]. However, the itch of cholinergic urticaria usually responds well to systemic antihistamines, attesting to the central role of histamine, derived from dermal mast cells, as a mediator.

Symptomatic Dermographism

This common physical urticaria can be easily diagnosed by demonstrating whealing and itching occurring almost immediately and linearly at the site of a blunt object such as a key, drawn firmly over clinically normal skin. More accurate assessment can be achieved using a spring-loaded 'dermographometer' which, if calibrated, allows application of a measured pressure to the skin. There are no proven systemic associations with dermographism, and the eruption is easily distinguished from the local whealing and itching of urticaria pigmentosa (cutaneous mastocytosis) – which also wheals and itches upon rubbing the skin – because the latter reaction only occurs in clinically abnormal skin. Unlike delayed pressure urticaria (vide infra) which develops at sites of local pressure, the whealing and itching of dermographism subsides within minutes. About 10% of CIU patients also have symptomatic dermographism [3].

Unlike cutaneous mastocytosis, the population density of dermal mast cells is within normal limits in this physical urticaria. Nevertheless, dermal perfusion studies have clearly demonstrated the release of histamine at sites of dermographism [13], and the lesions appear in the main to be straightforward histamine wheal responses, with a similar appearance, short time course and response to antihistamine treatment as would be expected with a wheal due to intracutaneous histamine injection. Passive transfer of reactivity to stroking of skin has been demonstrated using a patient's serum and a non-human primate recipient although the nature of this factor is unclear [14].

Delayed Pressure Urticaria

Delayed pressure urticaria rarely, if ever, occurs by itself; almost invariably it is associated with CIU, and 50% of CIU patients also have delayed pressure urticaria [3]. Whealing occurs 2–6 h after application of pressure perpendicular to the skin, and when it occurs spontaneously, it is usually at sites of pressure (waist band, palms, soles). Wheals may be itchy, painful, or both and each usually lasts of 24 h or more.

Delayed pressure urticaria is generally unresponsive to antihistamine treatment, and it is unlikely that histamine release plays a significant role. It is also associated with

mild chronic systemic symptoms (fatigue, arthralgia, myalgia). Because of these specific clinical features, it is not surprising that delayed pressure urticaria also appears to differ in its pathomechanism from other physical urticarias.

Histologically, delayed pressure urticaria is characterized by a fairly dense dermal infiltrate with eosinophil, with marked evidence of eosinophil degranulation [15, 16]. Pharmacological studies of lesional skin have revealed elevated tissue levels of interleukin-6, but levels of arachidonate metabolites (leukotrienes, prostaglandins) were similar in lesional versus non-lesional skin [17, 18]. Although the pathological features of delayed pressure urticaria resemble those of a late-phase cutaneous reaction [16], the aetiology is unknown.

Cold Urticaria

More research has been done on cold urticaria than on other physical urticarias, with the possible exception of solar urticaria. Cold urticaria is conventionally classified into *primary* or *secondary* varieties. *Secondary cold urticaria* is diagnosed in patients with an identified underlying cause (cryoglobulinaemia, cold agglutinaemia). Such patients may have a recent history of a virus infection (*Mycoplasma pneumoniae*, hepatitis B or C, glandular fever) or of a lymphoreticular malignancy. These aetiological factors have been well reviewed by Neittaanmaki [19]. Other patients, in whom no underlying cause is evident, are designated as having *essential cold urticaria*.

In both varieties, contact of skin or mucous membranes with cold surfaces or fluids including air and water causes immediate local whealing and itching, often associated with acute systemic symptoms of flushing, headache, faintness and, rarely, collapse. Fatalities have been reported due to anaphylactoid reactions in acutely cold-sensitive patients following sea-bathing.

Essential Cold Urticaria

This type is by far the most common, and mainly occurs in children and young adults.

Heterozygous serum deficiency of the protease inhibitor α_1 -antichymotrypsin has been identified in a few patients [20], but its significance is unclear. There is no evidence of cutaneous vasculitis [21], and the dermal mast cell population density is within normal limits. However, if skin of affected individuals is repeatedly challenged at the same site, evidence of vasculitis may develop [22], raising the possibility that circulating immunoreactants may be involved. Kaplan's group have published evidence that an autoimmune mechanism may be

involved, in which circulating autoantibodies against IgE cross-link the high-affinity IgE receptor (FcεR1) [23].

It is possible to obtain a profile of pharmacological activity released in cold urticaria by sampling venous blood from the antecubital vein draining from cold-challenged skin. Analysis [24, 25] reveals release of histamine in parallel with onset and development of cold-evoked whealing and itching. However, other pharmacological activity, including eicosanoids (prostaglandin D₂) and eosinophil chemotactic activity, has been identified and it is also likely, though not proven, that mast cell-derived cytokines are involved. Repeated challenge of the skin leads to refractoriness to cold, a fact that is used in cold tolerance treatment for cold urticaria [26], which presumably owes its effectiveness to depletion of mediators including histamine. In summary, it is likely that histamine release is mainly responsible for the itching of cold urticaria, but other mediators are probably responsible for the redness and whealing.

Secondary Cold Urticaria

The principal underlying causes which should be sought in a patient with cold urticaria have been itemized above. About 5% of all patients with cold urticaria turn out to have the secondary type.

Clinically the whealing response to cold may not differ significantly from that occurring in essential cold urticaria, although the time course may be considerably longer, and purpura may also be present, suggesting an underlying vasculitis.

Deposited cryoglobulins may be polyclonal (post-infection) or monoclonal (IgG or IgM) and complement activation may be involved [27]. In one report a patient with cold urticaria had a circulating cold haemolysin associated with positive syphilis serology [28].

Solar Urticaria

This rare physical urticaria is frequently misdiagnosed. Most patients referred to me with this diagnosis actually turn out to have the much more common polymorphic light eruption. Characteristically, patients with solar urticaria have immediate whealing in response to sun exposure which subsides in 15–30 min if the patient covers the affected skin. Itching is prominent, and the condition is often disabling despite absence of systemic symptoms. Although this physical urticaria can be successfully treated by repeated local sun or artificial light exposure to produce tolerance [29], it responds poorly to antihistamines.

Histological studies by Norris et al. [30] showed an upper dermal, predominantly perivascular neutrophil

and eosinophil leucocyte infiltrate at 5 min and 2 h after administration of a minimum erythral dose of solar-simulated irradiation. At 24 h, mononuclear cells were also seen, but only with higher dosages. The action spectrum for solar urticaria is variable, and patients may react to UVA, UVB or visible light [31]. Tolerance following repeated exposure is a feature of solar urticaria, and can be used as a mode of treatment [29]. Tolerant skin responds normally to intradermal histamine injection and to injection of the histamine-liberating agent, codeine. However, a single intradermal injection of irradiated serum elicits urticaria in unexposed but not tolerant skin and repeated injection of irradiated serum into unexposed skin causes tolerance to the eliciting irradiation. That solar urticaria is due to a photoallergen to which the patient develops IgE-mediated sensitivity seems likely on existing evidence. Tolerance may be due to elevation of mast cell degranulation threshold due to persistent occupation of photoallergen binding sites on mast-cell-bound IgE. Antihistamines are, however, of limited value, possibly causing some relief of the itch, but poorly effective against the rash. Other treatments have included tolerance therapy with a variety of different emission spectra, and plasmapheresis [32].

Urticarial Vasculitis

This important chronic urticaria, which may appear indistinguishable clinically from 'ordinary' CIU, is almost certainly underdiagnosed and it is now my practice to skin biopsy all patients with what is ostensibly CIU, but poorly responsive to antihistamines. Classically, urticarial vasculitis presents as a chronic urticaria, with or without angioedema, in which individual wheals, often tender to palpation, are persistent, lasting for more than 24 h, with inconsistent itch, and often leaving a stain in the skin due to purpura. A skin biopsy is essential to confirm the diagnosis.

Systemic symptoms include arthralgia and malaise. However, as indicated above, the clinical features may appear generally unremarkable. Urticarial vasculitis may turn out to be confined to the skin, but evidence of systemic involvement should always be sought. Underlying aetiological factors often emerge, including autoimmune connective tissue diseases, especially lupus erythematosus and Sjögrens syndrome, of which urticarial vasculitis may be a presenting manifestation, inflammatory bowel disease, virus infections including hepatitis B and C adverse reactions to drugs and paraproteinaemia.

Urticarial vasculitis is an immune-complex vasculitis, targeting the post-capillary venules in skin and mucous

membranes. Histologically, endothelial cell swelling and degeneration, neutrophil polymorphonuclears within the capillary or venular walls, neutrophil degranulation leading to the appearance of scattered interstitial 'nuclear dust' are common findings. Additionally, there is usually evidence of diapedesis of red blood cells through endothelium, fibrin deposition and there may increased numbers of eosinophils. Direct immunofluorescence findings on skin biopsy may include perivascular immunoglobulin and complement deposition, but this is variable, may also be seen in 'ordinary' chronic urticaria, and is not useful diagnostically. The molecular mediators of urticarial vasculitis have not yet been identified. It may, however, be safely assumed that neutrophil proteases, activated complement components, eosinophil granule proteins and mast cell products are involved to variable degrees. Early accounts of urticarial vasculitis emphasized depletion of serum complement components, but in practice this is an unusual finding in the average patient. Although urticarial vasculitis commonly causes staining of the skin, mainly due to haemosiderin, scarring rarely occurs. The reader is referred to a comprehensive review by O'Donnell and Black [33] for more details.

Chronic Idiopathic Urticaria

About 50% of patients with chronic urticaria have CIU; well over half of these also have mucocutaneous angioedema and over 40% have associated delayed pressure urticaria (vide supra). Individual wheals or angioedema, which may occur in any area of the skin or mucous membranes, fade after 12–18 h, leaving no mark, and pruritus is almost invariable. Patients rarely scratch urticarial lesions; they usually rub them, and this may cause bruising, but the surface of the skin is unbroken. Systemic complications, including abdominal and respiratory symptoms are rare [M.W. Greaves, A. Borcea, unpublished findings] although accompanying delayed pressure urticaria may be associated with arthralgia. Degree of disability is, however, often severe. Recent quality of life studies [34] have demonstrated that CIU causes impairment of social, occupational and domestic life comparable with that occurring in severe coronary heart disease. The average natural history of the disease is for eventual sustained remission in 2–3 years [35, 36] following a relapse-remission-relapse course.

The aetiology is traditionally elusive, hence the adjective 'idiopathic'. Most patients and their relatives believe that food ingredients are the cause. This can rarely be sub-

stantiated, and the diagnosis of a food item as a cause of chronic urticaria should not be made in the absence of confirmatory evidence from placebo-controlled challenge testing. Chronic 'focal' infections and infestations including candidosis and parasitosis have often been proposed, but without convincing evidence. Most recently numerous publications have appeared advocating *Helicobacter pylori* infection as causative in CIU. This topic has recently been reviewed [37]. Undoubtedly, *H. pylori* infection can be demonstrated in at least 30% of patients with CIU, but there is no convincing evidence that treating it makes any difference to the urticaria [38]. However, *H. pylori* may have an indirect aetiological role in autoimmune urticaria [37].

In a large subset of patients with CIU the cause of the urticaria has recently been demonstrated to be an autoimmune process involving functional (mast cell activating) anti-FcεR1 autoantibodies, and this has had significant consequences in terms of investigation, prognosis and management.

Pathophysiology

Direct analysis of histamine in tissue fluid of lesional skin in patients with CIU has confirmed the presence of elevated levels [1] and, although the overall population density of dermal mast cells is normal, dermal mast cell degranulation is present.

These facts, coupled with the observation of reduction of itch and whealing following H₁ antihistamine treatment, substantiate the involvement of histamine from activated dermal mast cells in the pathogenesis of the disease. However, the time course of the individual wheals and the histological features (vide infra) argue against histamine as the sole mediator, and it seems likely, though not proven that cytokines, proteases and eicosanoids also play a role.

Histological examination of lesional skin shows unremarkable appearances with a light perivenular and pericapillary infiltrate of predominantly mononuclear cells with a few neutrophils and eosinophils, variable oedema and fibrin deposition and no evidence of endothelial cell damage. Direct immunofluorescence examination is usually negative, but occasionally evidence of IgG or IgM deposition with a perivascular distribution may be seen. The pathology of chronic urticaria has recently been reviewed [15].

Autoimmune Urticaria

Arguably the only significant advance in understanding of the pathomechanisms of chronic urticaria in recent years has been the realization that at least in some patients with

CIU, the disease has an autoimmune basis [39]. As long ago as 1962, Rorsman [40] reported that peripheral blood basopenia is common in chronic urticaria and he speculated that 'it appears probable that antigen-antibody reactions or histamine liberating substances bring about degranulation of basophil leukocytes'. We have fully justified his speculation [41] and we and others later demonstrated that residual circulating basophils in CIU also showed evidence of desensitization in the shape of attenuated release of histamine following challenge in vitro by anti-IgE [42, 43]. Kaplan's group explicitly proposed an autoantibody mechanism for chronic urticaria in 1988 [23], but the first direct evidence for a circulating 'urticaria-evoking' factor in CIU was by Grattan et al. [44], who, in 1986, reported the presence of a mediator of CIU in patients' serum. We subsequently characterized this factor which turned out to be an IgG autoantibody directed against the α -chain of the high-affinity IgE receptor, Fc ϵ R1, or, less commonly, against IgE itself [39]. Subsequent studies by ourselves [45] and others [46–48] confirmed these observations and established that these autoantibodies were functional and causative in CIU. They cause whealing and itching upon autologous injection in patients' skin and release histamine from human donor basophils and mast cells, and their serum levels reflect disease activity [49, 50]. Not all patients with CIU can be demonstrated to have these autoantibodies; figures for the incidence range from 30% (London) to over 50% (South Carolina) and seem to depend on the sensitivity of the assay used (a rat basophil leukemia cell line transfected with the genes encoding for the α - and γ 1- and γ 2-chains of Fc ϵ R1 appears, in Kaplan's hands to be especially sensitive) and on population differences of CIU patients studied. These autoantibodies may be functional or non-functional. They can be detected by immunoblotting [51].

However, recent work has shown that activation of mast cells or basophils by anti-Fc ϵ R1 autoantibodies probably involves complement activation and that the correlation between functional (histamine-releasing) and non-functional (immunoreactive) anti-Fc ϵ R1 autoanti-

bodies is poor [52, 53]. Immunoreactive (non-functional) anti-Fc ϵ R1 autoantibodies can be found in sera of patients with autoimmune connective tissue diseases, autoimmune bullous diseases and in physical urticarias, but not in healthy individuals. Presumably non-functional but immunoreactive anti-Fc ϵ R1 autoantibodies fail to aggregate high-affinity IgE receptors, due to confirmational differences in the IgG autoantibody.

Demonstration of histamine release from healthy donor basophils or mast cells or a rat basophil leukaemia cell line expressing a functional receptor remain the gold standard for establishing an autoimmune basis in CIU. The IgG subtypes involved are predominantly IgG1 and IgG3 [51]. These findings do not, of course, exclude the involvement of other circulating factors, e.g. cytokines [54, 55] or mast-cell-specific factors for which we already have preliminary evidence [45]. The reason for lack of clinical evidence of extracutaneous mast cell activation is unclear, but it is worth noting that pulmonary mast cells, unlike dermal mast cells, do not express sites for complement activation.

The eruption of patients with autoimmune urticaria shows no distinguishing specific clinical or histological features from 'ordinary' CIU [56] although recent studies of the inflammatory cell infiltrate [15] suggest that eosinophil activation is more persistent in patients who do not have the autoantibody. The finding of exceptionally low peripheral blood basophil counts in patients with autoimmune urticaria has already been alluded to. In this context, the recent observation of accumulation of basophils in the skin of patients with CIU [57] is of interest and may reflect a significant role for these cells in the pathogenesis of CIU.

The clinical course of autoimmune urticaria, though not differing markedly from that in non-autoimmune patients, does tend to be prolonged and less responsive to routine antihistamine therapy. In severely affected patients, recourse may have to be made to treatment by immunotherapy, including cyclosporin, intravenous immunoglobulin or plasmapheresis [50, 58, 59].

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