CHRONIC URTICARIA

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Chronic urticaria (CU) is diagnosed when wheals, with or without concomitant angioedema, occur continuously or on a frequently recurrent basis for more than 6 weeks.[1,2] Despite many recent advances in the understanding of CU, the disorder remains a major challenge in terms of its aetiology, investigation and management.[3] The true prevalence of CU in South Africa is currently unknown, but figures for the UK and USA suggest a prevalence of <1% of the general population.[4] However, the Red Cross Children's Hospital (RCCH) Allergy and Dermatology Clinics recently managed to enrol 90 children with clearly defined CU over a 2-year period.[5] By comparison, acute urticaria affects approximately 15% of the general population, is usually a self-limiting disease and a causal trigger is more frequently established.

PATHOGENESIS OF CHRONIC URTICARIA

Regardless of the aetiology, CU is predominantly the result of cutaneous mast cell activation with subsequent liberation of chemical mediators. Histamine is the dominant mediator released which rapidly induces vasodilatation and capillary permeability. These histamine effects are clinically characterised by a wheal and flare response (Fig. 1). The flare reaction, which occurs far beyond the area of histamine diffusability is due to a histamine-induced axon reflex with secondary release of substance P from C nerve fibres. These fibres also initiate the afferent stimulus for the associated intense pruritus. Fortunately, histamine release is confined to the skin and sub-mucosa, thus the cardiovascular decompensation characteristic of anaphylaxis does not occur.

Biopsy of urticarial lesions reveals a prominent late-phase cellular reaction with perivascular infiltration of CD4 T lymphocytes, monocytes and a variable number of neutrophils and eosinophils.[6] Controversy exists as to whether the number of mast cells in CU lesions are elevated, but a generalised increase in histamine 'releasability' has been demonstrated.[7] Mast cell degranulation alone is insufficient to explain the entire clinical course, and therefore, like all late-phase allergic reactions, the perpetuation of the inflammatory response by cellular infiltrates is important. That other immune processes are involved in the pathogenesis of CU is substantiated by the observation that corticosteroid (CS) therapy rapidly achieves disease control, despite CSs having little effect on cutaneous mast cell degranulation.[8]

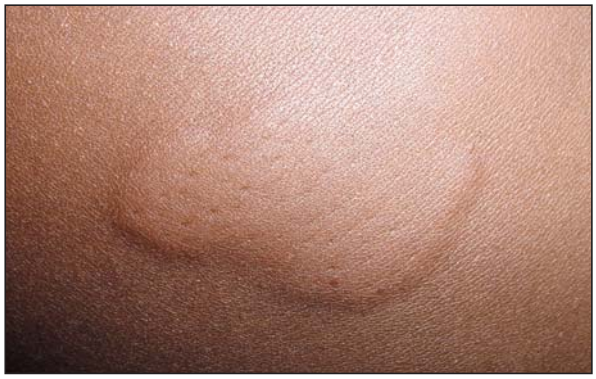

Fig. 1. Wheal and flare reaction.

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CLINICAL PRESENTATION

The presenting history of patients with CU usually centres around two fundamental complaints: itchy wheals and the physical disfigurement experienced as a result of the urticarial and/or angioedema lesions (Fig. 2). These two symptoms are almost entirely responsible for the low quality of life scores returned, with adult scores approximating those of ischaemic heart disease patients and paediatric scores equivalent to those of children with atopic eczema dermatitis syndrome (AEDS).[5] The intensity of itch experienced with urticarial wheals varies between patients. In keeping with the symptoms experienced in other allergic disorders such as asthma-associated cough, the itching is frequently worse at night. The observation has also been made that the itch of urticaria, unlike that associated with AEDS, is relieved by rubbing rather than by scratching. As a consequence the scratch marks and deep abrasions observed with AEDS are rarely seen in CU. Interestingly, itching is seldom if ever associated with angioedema alone. It is essential to ascertain wheal duration as the wheals of CU classically last no longer than 24 hours, while the wheal duration in urticarial vasculitis by definition should persist beyond 24 hours. Wheals induced by physical triggers such as pressure, cold, vibration, and water stimuli are usually transient and disappear within 2 hours.

Clinical examination reveals skin lesions which are transient, flitting, raised and intensely pruritic. The wheals vary in size and shape and frequently have irregular margins due to pseudopodia. They are typically indurated towards the periphery and are generally paler than the bright red of the surrounding skin because of the compressing effect of dermal oedema. 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, is the result of

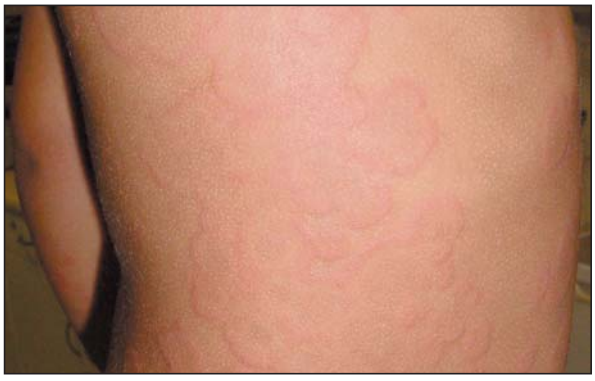

Fig. 2. Severe generalised urticaria.

increased arteriolar blood flow associated with a central wheal leading to deprivation of blood flow in the skin surrounding the lesion, i.e. 'steal' effect.[4,9] Urticaria may appear anywhere on the skin, including the scalp, palms and soles, but the mucous membranes are infrequently involved (unlike angioedema). Cold urticaria is the exception as the wheals may involve the tongue or palate following a local cold stimulus such as ice cream.

Angioedema can be defined as transient oedema of the dermis, subcutaneous tissue and/or submucosa. Angioedema accompanies urticaria in approximately 50% of adults and 80% or more of children (Fig. 3).[4,5] This strong association between angioedema and CU proves helpful if patients are asymptomatic at the time of presentation, as a history of both makes the diagnosis of CU likely. Angioedema typically affects the face (particularly the eyelids and upper lip), hands and feet. It is not uncommon for young boys to complain of swelling of the glans penis (Fig. 4) or for the labia to be involved in girls. Occasionally, there may be swelling of the tongue, pharynx or larynx, but the life-threatening airway compromise characteristic of hereditary angioedema has not been described in CU. It is particularly important to consider alternative diagnoses if patients present with angioedema alone. These include conditions like hereditary angioedema, laryngeal oedema and rarely severe oral allergy syndrome. The duration of swelling in angioedema is usually less than 24 hours, but larger swellings may take longer to subside.

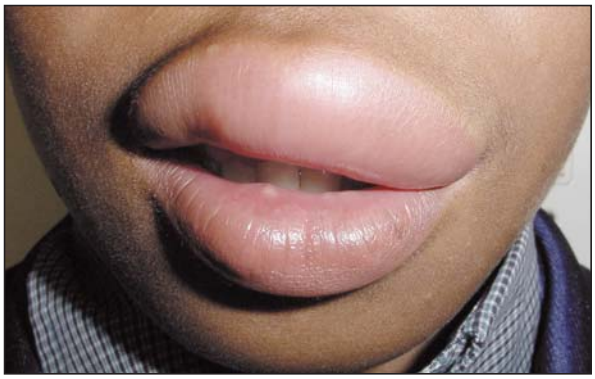

Fig. 3. Severe angioedema.

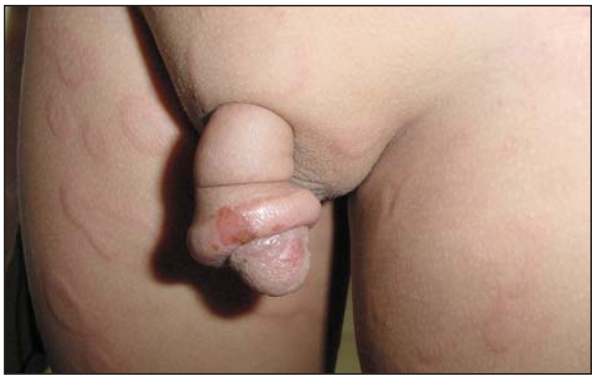

Fig. 4. Angioedema of the penis.

AETIOLOGY

The clinical history and physical findings may suggest an underlying cause of urticaria, but this is almost entirely restricted to the physical urticarias, outside of which the incidence of finding an exogenous cause is less than 1% (Table I).[4] However, patients with all variants of CU and particularly the physical urticarias are characteristically over-investigated, and there seems to be no end to the stream of novel quasi-scientific aetiological and management theories put forward. There are few published studies which adequately define the natural history and aetiological characteristics of CU in childhood.[10-12] Potential aetiologies include:

- **Physical urticaria.** The finding of a physical trigger is important as it obviates the necessity for investigation beyond any challenge testing required to confirm the diagnosis. The diagnosis of a physical trigger for CU is best made by means of a detailed clinical history. The physical urticarias are characterised by the development of wheals and itching which appears promptly after application of the appropriate physical stimulus. The exception is delayed pressure urticaria, where a period of 2 or more hours may elapse prior to the development of wheals in response to provocation. Unfortunately, more than one physical urticaria may afflict a patient concurrently; for example, symptomatic dermographism and cholinergic urticaria frequently occur simultaneously.[4] Characteristically the wheals of physical urticaria are transitory, lasting for only a few minutes or no more than 1-2 hours after removal of the provoking stimulus. Again, delayed pressure urticaria is an exception as wheals may last for 24 hours or more. After wheals have subsided, the affected skin is frequently refractory to further provocation for a period ranging from a few hours to a day or two. Wilfully inducing a refractory period may be of use to patients with physical urticarias such as cold urticaria and solar urticaria. In an attempt to standardise the classification and investigation of the physical urticarias, consensus guidelines for performing physical challenges have been published.[13]

Table I. Physical urticarias

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

- **Auto-immunity.** The most significant recent advance in the study of CU is the finding of functional circulating auto-antibodies in approximately 35-40% of both adults and children with CU.[5,14-16] The majority of these circulating functional IgG antibodies are directed against the IgE receptor (anti-FcεRIα), with an additional 5-10% having antibodies against the IgE antibody itself. These auto-antibodies induce wheal and flare reactions by activating basophils and mast cells, a process augmented by complement through the formation of C5a anaphylatoxin.[17] However, the findings of such functional auto-antibodies are specific for CU, and although present in conditions such as dermatomyositis, bullous pemphigoid and pemphigoid vulgaris they are non-functional. Interestingly, they have not been demonstrated in adults or children with AEDS.[5] The presence of circulating auto-immune factors can be crudely demonstrated by performing the autologous serum skin prick test (ASST) (Fig. 5).[4] The ASST involves the use of autologous serum intradermal injections. A positive test is suggestive but not diagnostic of an auto-immune basis for the patient's CU and confirmation is needed by *in vitro* testing of the patient's serum for anti-FcεRIα or anti-IgE auto-anti-

bodies.[4] However, the test is painful and poorly tolerated in children, particularly as topical anaesthetics interfere with interpretation. Spontaneous bradykinin release may occur during serum processing thereby increasing the incidence of false-positive results.[18] The ability of the test to predict for the more specific and costly auto-antibody tests is also limited, as only when all histamine-releasing factors and auto-antibody positive results are combined is a significant association shown.[5] More positive evidence of the value of ASST results would be required before this poorly standardised test would become routine practice in children.

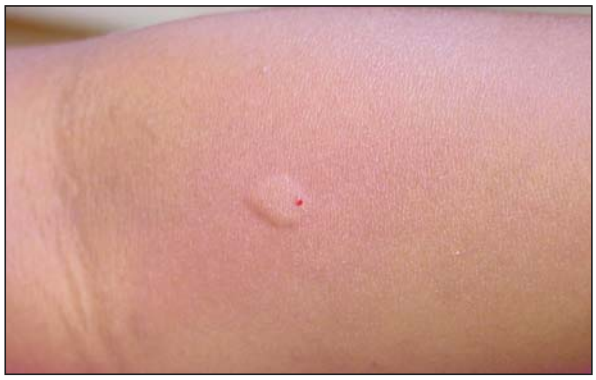

Fig. 5. The autologous serum skin-prick test.

- **Thyroid auto-immunity.** An association between CU and thyroid auto-immunity was initially made when an increased frequency of Hashimoto's thyroiditis was observed among adult CU patients.[6,19] Subsequently, an increased incidence of auto-antibodies to thyroglobulin or microsomal-derived antigen was demonstrated, almost exclusively in female patients. This association has until recently been largely restricted to adults but a recent analysis of 187 children with CU found 8 (4.3%) to have increased levels of antithyroid antibody.[20] All patients were female and 5 were euthyroid. Only 2 patients were diagnosed during the initial work-up for CU, neither of whom experienced resolution of CU symptoms in response to thyroxine therapy. The entire RCCH paediatric cohort was clinically euthyroid. Population surveys suggest that the prevalence of thyroid auto-immunity in children with CU may be higher than that of the general paediatric population.[21-23] Although it seems intuitive to normalise thyroid function tests, it may well be that these findings occur as parallel auto-immune events and are in no way causal. In a study population of 250 adult patients with CU, abnormal thyroid function (increased or decreased T4 and/or increased or decreased TSH) was detected in 19% while 27% had antithyroglobulin antibody, antimicrosomal antibody or both.[6] However, even in the absence of CU, there is no consensus on the most appropriate management.[24]
- **Allergy.** Prior to consultation, CU is nearly always perceived to be a manifestation of an allergic or idiosyncratic reaction to foods, food additives, or food dyes. There is however little evidence to sustain these suppositions.[25] To avoid the implementation of unnecessary elimination diets, food allergy tests must be carefully chosen. If positive results (skin-prick or serum IgE tests) identify candidate food allergens, their validity should be confirmed by making use of carefully controlled elimination and/or challenge diets. Elimination diets are occasionally helpful if a non-IgE pathway is suspected in the pathogenesis or if no IgE tests are available to the suspected agent, e.g. aromatic volatile ingredients in tomatoes, white wine and oily extracts from herbs. A small subset of patients with CU may experience exacerbations to these aromatic substances, shown not to be due to histamine, salicylate or direct mast-cell histamine release.[26] A negative elimination diet will often reassure patients and caregivers that food allergies are not causative.
- **Infective/parasitic causes.** There are no strong data either to support or refute the role of infections in CU. Of all the viral and parasitic causes incriminated to date, *Helicobacter pylori* and *Ascaris lumbricoides* intestinal infestation have been most extensively studied. Only 1 stool specimen analysed in the RCCH study revealed *A. lumbricoides* ova, but this patient had a negative specific *A. lumbricoides* IgE.[5] Acute urticaria is well described during the prodromal and acute stages of infectious hepatitis, but data supporting a causal association of hepatitis A, B and C infections in CU are not convincing.[6]
- **Drug-induced CU.** Various drugs have been incriminated in the aetiology of CU. Angiotensin-converting enzyme inhibitor (ACEI)-associated angioedema is well described, particularly upon reintroduction of ACEI therapy. It is also important to exclude non-steroidal anti-inflammatory drugs (NSAIDs) as a potential cause of urticaria and angioedema.[6]
- **Connective-tissue disorders and vasculitides.** Only occasionally will CU and angioedema be manifestations of an underlying connective-tissue disorder or systemic vasculitis in which the biopsy findings are consistent with a leukocytoclastic angiitis rather than the non-necrotising vasculopathy typical of CU.

Despite evidence for an auto-immune mechanism in many patients with CU, approximately 60% of cases still remain idiopathic, hence the frequent use of the term chronic idiopathic urticaria.

DIAGNOSTIC APPROACH

Beyond a thorough clinical examination, there are few, if any, diagnostic tests for CU. Many investigations have been shown to have a low yield; this is particularly so for allergy investigations, as patients with CU carry the same prevalence of food allergy as the general population. Full blood count, urine analysis, serum chemistry, globulin assays and liver function tests are typically normal. If a connective-tissue disorder is clinically suspected, measurement of the erythrocyte sedimentation rate (ESR), tests for antinuclear antibodies, and other serologic tests may be indicated. Complement determinations are not indicated to exclude hereditary or acquired deficiency of C1 inhibitor in patients with wheals and angioedema or wheals alone, as patients with hereditary or acquired deficiency of C1 inhibitor do not have wheals and return normal results. If measurement of C4 is low, this should be followed by a determination of the levels and function of C1 inhibitor. Given the association of CU with thyroid disease, thyroid-function tests including tests for antithyroglobulin and antimicrosomal antibodies may be helpful if clinically indicated. Very occasionally investigations may be required to exclude the presence of plasma cryoproteins in patients with cold urticaria. Food or food-additive allergies are so rarely a cause of CU that routine testing is not recommended unless the history suggests a particular allergen. Many patients and caregivers will only accept a limited diagnostic approach after detailed counselling. Only in highly atypical presentations is a skin biopsy helpful, e.g. associated fever, arthralgia, raised ESR, lesions lasting 36 hours or more, or associated petechiae or purpura.

Table II. Treatment principles

	1st line	Alternative/Add on
Mild urticaria and angioedema	Non-sedating H_1RA	High-dose non-sedating H_1RA
		Sedating H_1RA (e.g. diphenhydramine, hydroxyzine)
Severe urticaria and angioedema	High-dose non-sedating H_1RA	H_1RA H_2RA LTRA Doxepin (tricyclic antidepressant with H_1- and H_2-RA activity) Corticosteroids Other 'immune modifiers'
Severe angioedema	High-dose non-sedating H_1RA	Benadryl
		Diphenhydramine

H_1RA - H_1-receptor antagonists; LTRA - leukotriene receptor antagonist.

TREATMENT RECOMMENDATIONS

Given that histamine is the predominant mediator in CU, it makes therapeutic sense either to antagonise H_1-receptors with antihistamines or alternatively to modify the formation of mediating inflammatory cells with more potent anti-inflammatory agents. The goal of therapy is to maximise daily function with minimal, if any, use of systemic immune modifiers such as corticosteroids or cyclosporin (Table II).

- **Histamine H_1-receptor antagonists (H_1RAs).** The non-sedating antihistamines have demonstrated an ability to alleviate pruritus and decrease the incidence of wheals in most patients with CU. A common treatment error is for symptomatic patients to be maintained on regular antihistamine doses only. This seemingly 'resistant' sub-group of CU patients must be given a trial of high-dose non-sedating antihistamines prior to introducing a second agent. This approach is substantiated by the RCCH study where all but two patients achieved symptomatic control when using a higher daily dose of cetirizine for symptom flares. The mean dose of cetirizine required to gain symptomatic control was 0.42 mg/kg, which is higher than the safety data of 0.25 mg/kg for young children.[27] On this regimen 5 patients experienced probable adverse reactions: fixed drug eruption (1), hyperactivity (2) and drowsiness (2).[5] High doses of the older sedating antihistamines may occasionally achieve additional therapeutic benefit, e.g. hydroxyzine, diphenhydramine and cyproheptadine. Although patients may become accustomed to the sedating effects of these drugs, psychomotor performance may be significantly impaired and extreme care is required.
- **Combined H_1- and H_2-receptor antagonists.** Approximately 85% of histamine receptors in the skin are of the H_1 subtype, and the remaining 15% are H_2-receptors. The addition of an H_2RA to an H_1RA may therefore augment symptom control provided by high-dose H_1RA. Trials to date suggest that only a small additional benefit is to be gained by using this combination. Doxepin, a tricyclic antidepressant, blocks both types of histamine receptors and is a more potent inhibitor of H_1-receptors than either diphenhydramine or hydroxyzine. However, sedation is an even greater problem and limits the usefulness of this drug.
- **Leukotriene receptor antagonists (LTRAs).** The LTRAs have been shown to be superior to placebo in the treatment of patients with CU, but there are few data to support their use as single therapy. A small additional effect may be experienced once maximal H_1- and H_2-receptor blockade has been achieved.[28]
- **Corticosteroids.** CS therapy may be required to gain control if patients remain poorly responsive to a combination of H_1RA, H_2RA and the LTRAs. This effect occurs despite an apparent inability of CSs to inhibit mast cell degranulation and antigen-induced histamine release, which suggests a role for other non-histamine immune pathways in the pathogenesis of CU. There is little scientific rationale for the use of CS in certain physical urticarias, such as cold urticaria, where acute histamine release is the sole disease mediator of the rapidly disappearing urticarial wheals.[3]
- **Experimental therapies.** The use of other experimental therapies such as plasmaphoresis, cyclosporine, sulfasalazine, warfarin and androgens have occasionally achieved success, further substantiating the role of circulating immune factors in the pathogenesis of CU. Although controversial, treatment with levothyroxine has been proposed in euthyroid patients with antithyroid antibodies and CU.[3] These experimental therapies should ideally be administered in specialist centres.

In summary, the natural history of CU is favourable, especially in children; 39% (30/76) of the RCCH paediatric cohort achieved remission during the 3-year follow-up period. However adult studies suggest that the condition persists in 71% of patients at 5 years and 56% at 10 years.[29] For the majority of patients the use of appropriate doses of H_1RAs will achieve good symptomatic control. Useful adjunct therapies include H_2RA and LTRAs, both of which have few side-effects. Given that most patients with CU are otherwise healthy, laboratory testing is not usually indicated, and if performed should be evidence-based and goal-directed. When managing CU the adage 'less is more' seems appropriate, i.e. less investigations and more antihistamines.

Informed consent was obtained for use of patient photographs.

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