

Chronic urticaria and angioedema

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Summary

Of 231 patients evaluated for chronic urticaria and angioedema (CUA), 192 were diagnosed as having an idiopathic condition. The roles of serum IgE, complement (CH_{50}), and immune complexes (IC) were investigated in 112 patients with idiopathic CUA. Immediate skin tests were not helpful, but total IgE was elevated in 13%, equally divided between dermographic (D) and non-dermographic (ND) patients. Depressed haemolytic complement (CH_{50}) was noted in 10% of CUA, all of whom were D. Serum IC were elevated in 38%, equally divided between D and ND patients. There was no relationship between depressed CH_{50} and elevated IC. Skin biopsies, evaluated by both light and immunofluorescent techniques, were negative for all specimens tested.

The pathophysiology of idiopathic CUA is multifactorial, with a variety of immunological mechanisms involving serum IgE, CH_{50} , and IC. The relationship between depressed CH_{50} and dermographism was noted but unexplained by serum or tissue studies.

Introduction

Chronic urticaria and angioedema is a common disorder, usually idiopathic in origin. Such patients manifest transient, superficial weals and subcutaneous swellings. Pathologically, only oedema involving dermal and subcutaneous tissues is usually noted. Although such patients often receive complete evaluations, the aetiology can rarely be ascertained, and management is directed to control of symptomatology. (Thompson, 1968; Sheffer, 1975; Levine, 1975; Champion *et al.*, 1969).

This study reviews the pertinent clinical features of a large number of patients who presented with chronic urticaria and angiodema (CUA). In addition, extensive laboratory investigations were undertaken to try and elucidate the pathophysiology involved in those patients with idiopathic disease.

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Materials and methods

Patient evaluations

231 patients were evaluated at McGill University over a period of 4 years. All were referred by a wide variety of physicians within the community, and presented chronic or recurrent urticaria and/or angioedema of greater than 2 months duration. A complete history and physical examination was performed on each patient. Dermographia was assessed off medication a minimum of 48 hr by scratching lightly on the back and evaluating the weal and flare response 15–20 min later. No evaluation for delayed dermographia was made in any patient.

Laboratory evaluation

Each patient had epicutaneous testing for both inhalant and food allergens after antihistamines had been withheld for 48 hr. A CBC and sedimentation rate, routine biochemistry, chest roentgenogram and urinalysis were ordered on each patient. Special tests on many patients included serum complement, anti-nuclear antibody, total IgE, immune-complex determination and a skin biopsy evaluated by both light and immunofluorescent microscopy. When serum was inadequate or technically unsuitable, these patients were excluded. In selected patients, either an ice cube or exercise challenge was performed. Stool examinations for ova and parasites were performed in appropriate situations.

Laboratory techniques

Adequate blood samples were obtained from 112 of 192 patients with idiopathic CUA at the time of initial evaluation, and serum aliquots were subsequently stored frozen at -70°C . Total haemolytic complement (CH_{50}) was assayed, using the method of Kent and Fife (1963). Individual complement-components were measured by radialimmunodiffusion in agar (Fahey & McKelvey, 1965). Total IgE levels were determined using the radioimmunosorbent technique (Johansson, Bennich & Wide, 1968). Immune complexes were assayed using ^{125}I -C1q polyethylene glycol (PEG) precipitation, as modified by Zubler *et al.* (1976). Lesional-skin trephine-biopsy specimens were obtained, stained with haematoxylin and eosin and giemsa, and examined by light microscopy. Immunofluorescent studies were performed on each specimen to evaluate the presence of immune reactants using antisera mono-specific for IgG, IgM, IgA, Beta 1C, and fibrinogen.

Results

Table 1 reviews the results of the clinical evaluations of the 231 patients with chronic urticaria and angioedema. One patient presented with urticaria and, within a short period of time, a diagnosis of metastatic renal-cell carcinoma was confirmed. The patient subsequently died. Three patients became asymptomatic shortly after discontinuing medication. Subsequent challenges were not undertaken in these patients. Thirteen patients had clinical evidence for cold urticaria, confirmed by ice-cube challenge. Cholinergic urticaria was documented clinically in three patients. Eight patients had hyperthyroidism coincident with the onset of chronic urticaria. The hives improved only after successful treatment of hyperthyroidism. Four patients had polycythemia vera, the diagnosis antedating the onset of cutaneous eruptions. Seven presented with systemic signs and symptoms, including arthritis and/or arthralgias,

Table 1. Etiology of chronic urticaria and angioedema in 231 patients

Clinical evaluations	No. of patients
Malignancy	1
Drugs	3
Cold Urticaria	13
Cholinergic Urticaria	3
Hyperthyroidism	8
Polycythemia Vera	4
Vasculitis	7
Idiopathic	192

Table 2. Alterations of serum IgE, haemolytic complement and immune complexes in both dermatographic and non-dermatographic patients with chronic urticaria and angioedema

	Normal values	Total	Abnormal		Dermatographic (39)		Non-dermatographic (73)	
			Number	(%)	Number	(%)	Number	(%)
Elevated IgE	< 200*	112	14	13	8	19	6	8
Decreased CH ₅₀	120–180	112	11	10	11	28	0	0
Elevated immune complexes	< 0†	112	43	38	14	36	29	40

* = u/ml; † = % binding.

suggesting a vasculitic variant of urticaria. In the remaining 192 patients no specific underlying diagnosis was elicited, and 112 of these patients had blood samples further analysed for abnormalities of serum total IgE, complement and immune complexes.

Patients with the idiopathic variety were further subdivided into those with, and those without dermatographia. Forty-four had significant dermatographia within 15 min. of scratching.

The role of IgE-mediated mechanisms was evaluated by means of epicutaneous-skin testing and serum total IgE. Occasional patients had skin reactivity to a multiplicity of allergens, including irrelevant inhalant and food allergens. There were no patients where a specific diagnosis of a food or inhalant allergy could be correlated with skin-test positivity. Elevated serum total IgE, defined by values above 200 u/ml, was detected in fourteen patients (Table 2), and did not correlate with the results of skin testing. There was a somewhat higher number of dermatographic patients with elevated total IgE (19% versus 8%) (Table 2).

There were eleven patients who had diminished serum haemolytic complement, and each of these patients was dermatographic (Table 2). Normal values were between 120–180 haemolytic units. Therefore, 25% of all dermatographic patients had hypocomplementaemia, but further evaluation of complement components did not indicate

whether this was mediated by the classical or alternative pathway. Immunochemical determinations of C3, C4, C1, C5, and C3-proactivator did not reveal any depressions of the various components in any patients. Follow-up blood samples were obtained in only four of these eleven patients while in remission. Each of these patients had normal complement levels at that time.

Elevated levels of serum circulating immune-complexes were detected in forty-three patients (Table 2). This group had a percentage binding of ^{125}I -C1q greater than two standard deviations above the mean of a control population. These were equally distributed between dermographic and non-dermographic patients. There were no distinguishing features clinically to separate these patients from those with normal immune-complex levels. None had fever, weight loss, arthralgias, or urticarial lesions suggestive of a vasculitic disease. Only three of the eleven hypocomplementaemic patients had elevated levels of immune complexes, suggesting little relationship between serum complement and immune-complex determinations.

Skin biopsies of urticarial lesions were performed on twenty-seven patients, including twelve with dermographia. No significant abnormality was detected by either light or immunofluorescent microscopy on any patient. A mild increase in mast cells was noted in three dermographic patients, but this was not considered to be significant. No patient with depressed serum-complement or elevated levels of serum immune-complexes showed evidence of microscopic abnormalities, although not all patients in each group were evaluated.

Discussion

The majority of patients with chronic urticaria and angioedema have an idiopathic disease process which usually improves either spontaneously or in response to medication (Thompson, 1968; Scheffer, 1975; Levine, 1975; Champion *et al.*, 1969). Although a number of underlying aetiologies can often be elucidated on careful evaluation, most patients appear to be in good health without any other evidence for significant disease processes. The mechanism of urticarial formation has been investigated by many authors, but the conclusions are quite variable. (Thompson, 1968; Sheffer, 1975; Levine, 1975; Champion *et al.*, 1969).

Our evaluation of 231 patients revealed that only 17% of all patients would be classified as non-idiopathic, consistent with other large series (Thompson, 1968; Sheffer, 1975; Levine, 1975; Champion *et al.*, 1969). Our objective was to investigate more completely the idiopathic variety of urticaria in order to clarify some of the possible immunological mechanisms. Twenty-three per cent of our patients with idiopathic disease were dermographic and constituted a significant sub-population. These patients often manifested somewhat different clinical features, in that their hives were exacerbated by scratching, hot water, pressure and a variety of other non-specific physical stimuli. Their hives were often linear in nature, but there were no other distinguishing features on clinical evaluation.

Skin testing of dermographic patients is notoriously unreliable, but epicutaneous testing seemed to diminish the incidence of non-specific reactivity. There was no evidence that our dermographic patients had more epicutaneous reactions. The incidence of elevated total serum IgE levels was higher in the dermographic group, and they may have an IgE-mediated disease process in some cases. Transfer studies have demonstrated that IgE antibodies can elicit dermographia in patients previously unreactive (Newcomb *et al.*, 1973). A role for IgE in chronic urticaria remains

controversial, as there are a number of contradictory studies (Juhlin, 1969; Kern & Lichenstein, 1976; Greaves *et al.*, 1974).

Although IgE-mediated mechanisms of mediator release from mast cells have classically been recognized as being involved in the pathophysiology of urticaria, a number of recent studies has suggested that other mechanisms may be of primary importance. (Berrens, Jankowski & Jankowski-Berntsen, 1976; Sissons *et al.*, 1974; Balbow & Ward, 1975; Chodirker, Bauman & Komar, 1979; Mathison *et al.*, 1977; Soter, 1977; McDuffie *et al.*, 1973; McLean *et al.*, 1980; Zeiss *et al.*, 1980; Phanupak *et al.*, 1980). Activation of complement, with subsequent anaphylatoxin formation may lead to mediator release. Hypocomplementaemia has been noted in a sub-population of urticaria patients, and activation by both or either classical or alternative pathways documented (Sissons *et al.*, 1974; Balbow & Ward, 1975; Chodirker *et al.*, 1979; Mathison *et al.*, 1977; Soter, 1977; McDuffie, 1973; McLean *et al.*, 1980; Zeiss *et al.*, 1980; Phanupak *et al.*, 1980). Those patients with classical-pathway-activation often have a vasculitis-like clinical presentation, differing clinically from the idiopathic variety of chronic urticaria. Our studies revealed that depressed serum complement, without evidence for specific-pathway-activation, does occur in a significant subpopulation of patients. All these patients were dermographic, and it is possible that the two conditions, i.e. hypocomplementaemia and dermographia, may be causally related. Recently, a skin biopsy from a dermographic patient with urticaria revealed evidence of a necrotizing vasculitis (Soter *et al.*, 1978). However, no abnormalities on skin biopsy were noted in any of our dermographic patients with, or without hypocomplementaemia. In addition, our hypocomplementaemic group did not show higher levels of circulating immune-complexes. Hypocomplementaemia in our patients would appear not to be related to immune-complex activation but indicative of another mechanism, possibly via the alternative pathway.

Elevated levels of circulating-immune complexes by various techniques have been detected in a large number of disease entities (Barnett *et al.*, 1979; Schur, 1978). Recent studies of biopsy specimens from some patients with chronic urticaria have revealed a number of immune reactants, suggestive of a possible immune-complex aetiology (Mathison *et al.*, 1977; Soter, 1977; McDuffie *et al.*, 1973; McLean *et al.*, 1980; Zeiss *et al.*, 1980; Phanupak *et al.*, 1980). In addition, one author has documented elevated levels of serum immune-complexes in chronic urticaria (Mathison *et al.*, 1977). Thirty-eight per cent of all our patients with idiopathic urticaria had elevated levels of circulating immune-complexes. None of these patients had clinical evidence for immune-complex disease, and skin biopsies in a number of these patients revealed no evidence for any abnormalities. However, it is well known that such immune reactants are transient, and inappropriate timing of the biopsy specimens may lead to false negative results. Patients with elevated immune-complexes were equally distributed between dermographic and non-dermographic patients, and these values were not related to depressions in haemolytic complement.

In conclusion, complement activation may be important in the pathophysiology of some patients with chronic urticaria and angioedema, but it is most probably not related to immune-complex formation. Hypocomplementaemia was associated with dermographia, but the relationship is somewhat unclear. Circulating immune complexes are present in large numbers of patients with urticaria, and may lead to release of mediators from mast cells by unknown mechanisms. We could not detect any immune-complex formation in tissues or activation of the classical pathway of complement to

account for mediator release. The pathophysiology of chronic urticaria and angioedema is probably multifactorial, including a number of immunological mechanisms.

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