

Immunological parameters and α_1 -antitrypsin chronic urticaria

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Summary

Serum immunoglobulins, complement and α_1 -antitrypsin were assayed in forty-eight patients with chronic urticaria. Thirteen cases had chronic cold urticaria and thirty-two had chronic idiopathic urticaria. Elevated mean serum IgM was found in chronic cold urticaria. Seven patients had partial immunoglobulin deficiencies. IgE was elevated in sixteen cases of chronic idiopathic and in two with chronic cold urticaria. Eight patients had depressed serum total haemolytic complement activity. Low C3 and normal C4 serum protein concentrations in four cases suggested alternative complement pathway activation. Twenty of forty-six patients were atopic, although specific allergies responsible for the urticaria were not identified in any of them. α_1 -antitrypsin levels were normal in all patients. The data suggest that the aetiology and pathogenesis of chronic urticarias in this study are heterogeneous. No evidence of abnormality of the protease inhibitor system in either chronic idiopathic or chronic cold urticaria was found.

Introduction

Chronic urticaria is a common disorder in which aetiology and pathogenesis are poorly understood (Matthews, 1974). In most cases, extensive clinical and laboratory evaluation rarely detects the aetiology or determines the underlying pathogenetic mechanisms.

Chronic urticaria may occur secondarily to underlying disorders including virus infections, collagen-vascular diseases such as systemic lupus erythematosus and immunoproliferative diseases including lymphomas. Patients with these conditions often manifest immunological abnormalities including autoantibodies, abnormal complement activity, monoclonal gammopathies and cryoglobulinaemia (Constanzi, Coltman & Donaldson, 1969). However, these underlying disorders are found infrequently in patients with chronic urticaria. In some instances, provoking factors,

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including exposures to cold, sunlight, vibration or skin pressure, are recognized and may be necessary prerequisites to the outbreak of urticaria. The requirement for a provoking physical factor, however, provides no insight into the underlying aetiology or pathogenesis.

In contrast to chronic urticaria, acute urticaria is characterized by the identification of specific allergies to foods, drugs, venoms, etc., in a high proportion of cases. Despite the failure to clearly identify specific allergies in most cases, it is commonly assumed that chronic urticaria is also allergic in origin and identical to acute urticaria except for the duration of symptoms. The validity of this assumption is questionable in view of the paucity of supporting evidence. Allergic mechanisms appear to be involved in some types of chronic urticaria, as the evidence of successful passive transfer (P-K-like reaction) of cold urticaria and the demonstration of IgE mediation of the reaction in some cases shows (Houser *et al.*, 1970; Wanderer *et al.*, 1971).

Reports of immunoglobulin, complement and α_1 -antitrypsin (α_1 -AT) abnormalities in some patients with chronic urticaria suggest new avenues of investigation. Elevated IgG and IgM were reported by Mines, Levine & Fireman (1969) and by Brown, Hermance & Choi (1974). Immunoglobulin deficiencies in chronic urticaria were noted by Buckley & Dees (1967). Recently, patients with idiopathic chronic urticaria have been described with abnormalities of complement activation and complement component serum concentrations by Sissons *et al.* (1974), Laurell, Martensson & Sjöholm (1975) and by Mathison *et al.* (1977).

Decreased levels of serum protease inhibitors, including α_1 -AT, have been reported in patients with cold urticaria and angioneurotic oedemas by Doeglas & Bluemink (1975). Acute depression of serum α_1 -AT has been described in two patients during provoked attacks of cold urticaria (Martens & Berrens, 1975). These reports suggest that an abnormality of the serum protease inhibitor system may be involved in the pathogenesis of this disorder.

We have surveyed patients from our clinical population with chronic idiopathic urticaria (CIU) and with chronic cold urticaria (CCU) for abnormalities of immunological parameters and of α_1 -AT. Abnormalities of serum immunoglobulins and of complement were found, but α_1 -AT abnormalities could not be demonstrated.

Materials and methods

Forty-eight patients were studied in the Clinical Immunology and Allergy Clinic at the University Hospital, London, Canada. All presented with chronic or recurrent urticaria of 3 or more months' duration. Despite thorough investigation, no allergic factors or relevant underlying disease could be identified in any case. Thirty-five patients were assessed as having CIU. In this group there were twenty-three males and twelve females ranging in age from 7 to 65 years, with a median age of 29 years. Thirteen additional patients had classical histories of acquired CCU. Eight out of eleven in this group who were tested developed wealing on the forearm after direct contact with an ice cube for 5 min. The CCU patients included six males and seven females ranging in age from 15 to 58 years, with a median age of 27 years. Nineteen healthy hospital personnel served as controls.

Blood samples were obtained from all patients at the time of initial consultation and serum aliquots were stored frozen at -20°C . Total haemolytic complement was determined on fresh serum maintained frozen at -70°C . Most immunological deter-

minations were carried out at the time of initial clinical workup. IgE and α_1 -AT levels were determined in batch testing on stored frozen serums.

Immunoglobulins G, A and M (IgG, IgA and IgM), complement proteins (C3 and C4) and α_1 -AT were assayed by single diffusion in agar by the method of Fahey & McKelvey (1965), employing immunoplates obtained from Meloy Laboratories. Immunoglobulin E was assayed by the radioimmunosorbent technique with Phadebas kits obtained from Pharmacia company (Johansson, Bennich & Wide, 1968). A search for monoclonal proteins was made by serum protein electrophoresis on cellulose acetate and microimmunoelectrophoresis in agarose gel. Cryoglobulins were looked for in fresh serum refrigerated at 4°C for 5 days. Total haemolytic complement activity (CH₅₀) was assayed kinetically by a modification of the method of Mayer (1971).

Data were analysed by Student's *t*-test or, where appropriate, by the two-sample rank test for non-parametric data. Comparisons were considered significant when a *P* of less than 0.05 was obtained.

Results

Immunoglobulins

No significant differences were observed in the mean IgG and IgA between patients with CIU, CCU and controls (Table 1). The mean IgM in the CCU group, 196 mg/100 ml, is substantially higher than the mean of 140 mg/100 ml found in the control group, and is significantly higher than the mean of 146 mg/100 ml in patients with CIU (Fig. 1). No monoclonal immunoglobulins and no cryoglobulins were detected in any serum. One patient with CCU had low IgG and IgA (460 mg/100 ml and 35 mg/100 ml respectively) while two other CCU patients exhibited isolated partial IgA deficiencies (35 and 55 mg/100 ml respectively). Two CIU patients had IgA deficiencies (42 and 44 mg/100 ml respectively), while one was deficient in IgG (480 mg/100 ml) and another in IgM (40 mg/100 ml). No underlying clinical disorders which might account for the low immunoglobulin levels were identified in any case.

Patients with CIU had mean serum IgE of 235 u/ml, which was substantially higher than the mean of 107 u/ml for CCU patients. The difference, however, was not statistically significant.

Complement

Total haemolytic complement activity and C3 and C4 protein concentrations did not differ significantly between urticaria groups and controls (Table 1). Eight patients, five with CCU and three with CIU, exhibited abnormalities of complement activity or of complement component concentrations (Table 2). All eight of these cases had depressed CH₅₀. Three had slightly low C3 while one exhibited a markedly and persistently depressed C3. In all instances, C4 was well within the normal range. One or more immunoglobulins was abnormal in four out of five patients with CCU and in two out of three with CIU who exhibited complement abnormalities. No consistent pattern of immunoglobulin abnormality was evident. It is noteworthy that two patients with complement abnormalities (Nos 2 and 3) were clinically atopic with elevated serum IgE.

Table 1. Immunoglobulins and complement in patients with chronic urticaria

Diagnosis	Patients (number)	Immunoglobulins				Complement		
		IgG (mg/100 ml)	IgA (mg/100 ml)	IgM (mg/100 ml)	IgE (u/ml)	Total haemolytic units (CH ₅₀)	C3 (mg/100 ml)	C4 (mg/100 ml)
Chronic idiopathic urticaria	35	1074 ± 282	184 ± 107	146 ± 59	235 ± 399	117 ± 29	140 ± 45	34 ± 10
Chronic cold urticaria	13	1095 ± 311	156 ± 98	196 ± 71*	107 ± 67	89 ± 23	132 ± 31	30 ± 9
Controls	19	1093 ± 265	200 ± 110	140 ± 66	n.d.	97 ± 15	140 ± 24	27 ± 7

n.d. = Not done; standard errors of means shown.

* $P < 0.05$, compared with CIU.

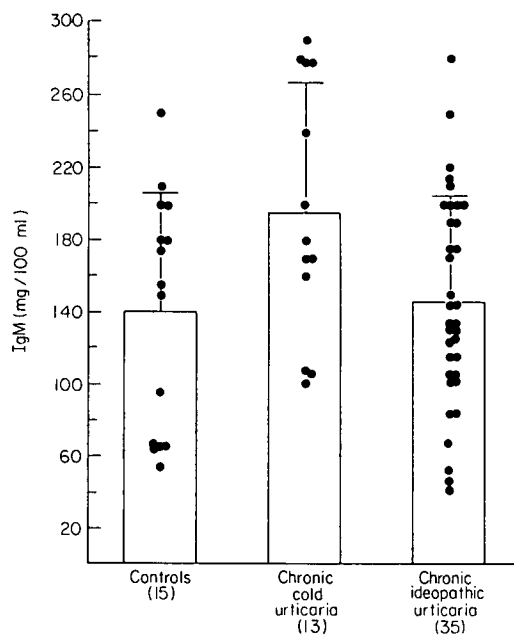


Fig. 1. Serum IgM in patients with chronic idiopathic urticaria and chronic cold urticaria. Means and standard errors are indicated. Numbers in parentheses show the number of patients studied.

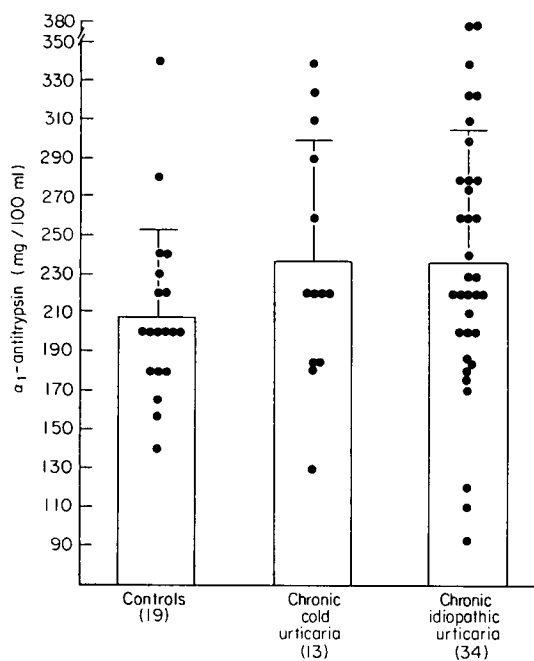


Fig. 2. Serum α_1 -antitrypsin in patients with chronic idiopathic urticaria and chronic cold urticaria. Means and standard errors are indicated. Numbers in parentheses show the number of patients studied.

Table 2. Immunoglobulins and complement in patients with chronic urticaria exhibiting complement abnormalities

Patient number	Diagnosis	Sex	Age (years)	Immunoglobulins					Complement		
				IgG (mg/100 ml)	IgA (mg/100 ml)	IgM (mg/100 ml)	IgE (u/ml)	Total haemolytic (CH ₅₀)	C3 (mg/100 ml)	C4 (mg/100 ml)	
1	CIU	M	42	1100	240	190	100	56	37	34	
2	CIU	F	47	700	330	200	300	61	110	40	
3	CIU	M	22	1250	300	100	205	69	82	35	
4	CCU	F	58	460	35	170	40	77	88	32	
5	CCU	M	27	950	33	105	40	65	80	35	
6	CCU	F	15	1125	145	278	80	52	125	22	
7	CCU	F	30	1600	265	200		56	160	30	
8	CCU	F	40	1100	150	180	12	75	95	28	
Normal range				710-1540	60-490	37-204 (M) 42-261 (F)	200	80-160	89-143	11-39	

CIU = Chronic idiopathic urticaria; CCU = chronic cold urticaria; abnormal values are in bold.

α_1 -antitrypsin

No significant differences in the serum levels of α_1 -AT were observed between CCU and CIU patient groups and the normal controls (Fig. 2).

Discussion

Serum immunoglobulin levels in patients with chronic urticaria vary widely. Mines *et al.* (1969) found elevated mean serum IgG in twenty-four patients with chronic urticaria while Brown *et al.* (1974) observed normal serum IgG but significantly elevated IgM in similar patients. In our investigation, the mean serum IgG and IgM in CIU patients did not differ significantly from control values. In CCU patients, however, the mean serum IgM was substantially higher than normal and significantly higher than in CIU patients.

The interpretation of variably increased serum immunoglobulins in patients with chronic urticaria observed in this study and in earlier reports is unclear. The first antibody readily demonstrable following antigenic stimulation is IgM. Elevation of total serum IgM suggests the presence of acute immunological stimulation. An increase in serum IgG implies more prolonged or chronic immunological stimulation than that present when IgM alone is elevated. Immunological stimulation may occur in a variety of circumstances, most notably with infection. No sources of immunological stimulation and no evidence of infection was identified in our patients or noted in earlier reports. It may be postulated, however, that elevated IgM and/or IgG indicates that the patient had undergone antigenic stimulation even though the source of the stimulation was not recognized.

Buckley & Dees (1967) reported sixteen children with histories of recurrent infections who presented with CIU. Nine of the sixteen were found to have deficiencies of one or more immunoglobulin type. The authors speculated that urticaria was secondary to infection and immunodeficiency. Only one out of the eighty-four patients included in the series reported by Mines *et al.* (1969) and by Brown *et al.* (1974) had an immunoglobulin deficiency, although seven out of forty-eight patients in the present series had one or more low serum immunoglobulins. In contrast to the children reported by Buckley & Dees (1967), all immunoglobulin-deficient patients in the current series were adults aged 18 to 58 years. Three presented with CCU and four with CIU. Although none had histories of undue susceptibility to infection, the possibility of clinically inapparent infection contributing to the pathogenesis of their chronic urticaria cannot be excluded.

The prevalence of atopy among the patients studied was evaluated. A personal history of seasonal or perennial rhinitis, or asthma, clearly attributable to allergic factors and a serum IgE level in excess of 200 u/ml in the absence of any non-atopic explanation for the high IgE were considered primary atopic characteristics. Secondary atopic criteria included a history of acute urticaria and/or angioedema attributable to specific allergenic exposures, well-defined food allergies, atopic dermatitis and a strong family history of atopic disease. Skin tests, which were not done in all cases, were excluded from consideration. Patients were considered atopic if they exhibited two or more primary characteristics, one primary and one or more secondary features or a minimum of three secondary features in the absence of any primary atopic characteristics.

Based on these criteria, fifteen out of thirty-four (44%) CIU patients and five out of twelve (42%) CCU patients were atopic. Three additional CIU patients who were

considered to be non-atopic had unexplained increases in serum IgE and are suspect atopic individuals. A high incidence of atopy in patients with chronic urticaria has been noted previously by Matthews (1974), and suggests that unrecognized allergic factors and a pathogenetic mechanism involving IgE may be involved in the development of urticaria in many of these patients.

The value of serum IgE determinations in the assessment of atopic disorders has been noted by Johansson, Bennich & Berg (1972). More recently, Nye *et al.* (1975) found 63% of atopics with an IgE level greater than 100 u/ml but only 1.7% of non-atopic individuals with their IgE exceeding 100 u/ml. Investigations in this laboratory on well defined atopic and non-atopic populations have generally confirmed these reports. In our hands, non-atopic individuals exhibit IgE greater than 200 u/ml only rarely in the absence of a non-atopic explanation, such as parasitic infestation or Aspergillosis.

In this study, serum IgE exceeding 200 u/ml was noted in sixteen out of thirty-four (47%) CIU patients. In contrast, Juhlin *et al.* (1969) found IgE greater than 400 ng/ml (approximately equivalent to 200 u/ml) in only three out of eighteen (17%) cases of idiopathic chronic urticaria. In our study, only two out of thirteen (15%) CCU patients exhibited elevated serum IgE.

Serum complement abnormalities have been reported in patients with both acute and chronic urticaria. Urticaria and angioedema were described by Glovsky *et al.* (1976) in a patient with an acute hypersensitivity reaction to procarbazine. McDuffie *et al.* (1973) reported four cases of chronic urticaria and synovitis associated with activation of the early components of complement, suggesting the presence of an immune complex disease. A multisystem disease with chronic urticaria, necrotizing vasculitis and hypocomplementaemia was described by Feig *et al.* (1976). Cold urticaria associated with lymphosarcoma, monoclonal cryoglobmopathy and activation of the early complement components was reported by Constanzi *et al.* (1969).

Abnormalities of the complement system with idiopathic chronic urticaria have been reported only recently. Ballow *et al.* (1975) studied 152 patients with idiopathic urticaria and angioedema and found two with low C1 and four others with subnormal C3. Of 200 CIU patients studied by Laurell *et al.* (1975), twelve exhibited low serum levels of C1q. Thirty others had abnormal electrophoretic heterogeneity of C1s while six were found with low C4. In contrast to these reports, Berrens, Jankowski & Jankowski-Berntsen (1976) failed to detect any abnormality of C1q, C4, C2, C3, C5 or C3 proactivator in thirteen cases, while Heitman & Daum (1973) found elevated C3 and C4 in similar cases.

In the current study, complement abnormalities were demonstrated in five out of thirteen patients with CCU and in three out of thirty-five cases of CIU, all of whom manifested depressed CH₅₀. Unlike the cases described by Laurell *et al.* (1975), normal C4 was found in all patients, arguing against the presence of immune complex disease. None of these cases clinically resembled the patients with chronic urticaria and synovitis described by McDuffie *et al.* (1973), and none had lymphoproliferative disorders with monoclonal gammopathies or cryoglobulinaemias.

A pattern of depressed CH₅₀ with low C3 and normal C4 observed in four cases suggests activation of the alternative complement pathway. A variety of substances, especially microbial polysaccharides, are known activators of the alternative sequence. It may be postulated that subclinical infection in these patients may have stimulated alternative pathway activation, leading to mediator release and urticaria. In two cases

of CCU (Nos 4 and 5, Table 2), partial IgA deficiency may have enhanced susceptibility to infection. Patients with complement abnormalities could not be distinguished clinically from those with normal complement, and no underlying disorders which might account for the complement changes were identified clinically. The findings in this investigation and in earlier studies suggest that evaluation of the complement system in patients with chronic urticaria may yield new insights into the aetiology and pathogenesis of these disorders.

The data may be interpreted to suggest that patients with CIU and CCU are heterogeneous with respect to aetiology and pathogenesis. Although causal allergens could not be identified in any of these cases, the high incidence of atopy in patients with chronic urticaria suggests that allergic mechanisms involving the IgE-mast cell system may be involved in the pathogenesis of the urticaria in many of these patients. In other largely non-atopic individuals, complement activation by the alternative pathway may lead to mediator release and urticaria. Other presently unknown mechanisms may be responsible for the disorder in a residual group who manifest neither atopic features nor complement abnormalities. Some overlap between these groups may also occur. In this study, two out of eight atopic patients also exhibited complement abnormalities.

Deficiency of serum proteolytic enzyme binding activity and α_1 -AT has been reported in patients with CCU and led Doeglas & Bluemink (1975) to speculate that this abnormality may characterize a subgroup of CCU patients predisposing them to the development of urticaria on cold exposure. In this investigation, normal levels of α_1 -AT were found in patients with both CCU and CIU. The discrepancy between these data and the earlier study likely results, at least in part, from the different criteria used in selecting controls. Serum concentrations of α_1 -AT increase in response to infections, inflammation, stress and some drugs, indicating an acute phase reaction (Lieberman, Mittman & Kent, 1971). In this series, the control group included only completely healthy individuals. In contrast, controls in the earlier series included patients with dermatological diseases, several of whom had high serum α_1 -AT concentrations, suggesting the presence of acute phase responses and resulting in spuriously high control values. Consequently, in the earlier series, an invalid comparison of α_1 -AT levels between CCU and controls may have been made. We conclude that abnormalities of α_1 -AT levels have not been convincingly demonstrated in patients with cold urticaria.

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