Acta Derm Venereol 2004; 84: 288–290

Taylor & Francis
healthsciences

CLINICAL REPORT

Chronic Idiopathic and Chronic Autoimmune Urticaria: Clinical and Immunopathological Features of 68 Subjects

Marzia CAPRONI, Walter VOLPI, Barbara GIOMI, Carla CARDINALI, Emiliano ANTIGA, Lucilla MELANI, Alberino D'AGATA* and Paolo FABBRI

*Department of Dermatological Sciences, II Dermatological Clinic and *Department of Nuclear Medicine, University of Florence, Florence, Italy*

Skin tests with autologous serum elicit an immediate wheal-and-flare response in about 30–50% of chronic idiopathic urticaria subjects, suggesting that an autoimmune mechanism might be involved in the pathogenesis of this disease. The aim of the present work, involving 68 subjects with chronic idiopathic urticaria, was to distinguish between the serum-positive and serum-negative cases and highlight the clinical differences between the two groups on the basis of the Breneman scale score. We also tried to correlate the finding of a positive response to the autologous serum skin test with other autoimmune diatheses or fully developed autoimmune disorders. Our results did not demonstrate any significant differences between the two groups with regard to mean age, sex distribution, angioedema and mucosal/cutaneous atopy. However, all subjects with positive autologous serum skin test presented more severe clinical features than serum-negative subjects. We found no differences between the two groups in the incidence of autoimmune disease. *Key words: chronic urticaria; autologous serum skin test; autoimmunity.*

(Accepted January 16, 2004.)

Acta Derm Venereol 2004; 84: 288–290.

Dr Marzia Caproni, Department of Dermatological Sciences, II Dermatological Clinic, University of Florence, Via degli Alfani 37, IT-50121, Florence, Italy. E-mail: marziacaproni@virgilio.it, fabbri@unifi.it

Chronic idiopathic urticaria (CIU) is a skin disorder characterized by the recurrence of eruptive and itchy wheals of at least 6 weeks' duration. Although no causes for mast cell and basophil degranulation can be found in most CIU subjects, studies by Grattan et al. (1) and Greaves (2) in recent decades have suggested that some autoimmune mechanism might be involved in a distinct subset of the disease, i.e. so-called chronic autoimmune urticaria. In fact, these authors and several other researchers established that an autologous serum skin test (ASST) elicits an immediate wheal-and-flare response in 30–50% of CIU cases, and later they confirmed *in vitro* that such histamine-releasing activity of CIU sera may be induced by circulating IgG against IgE and/or high affinity IgE receptor (FcεRI) (1–4). Studies on several case series (5, 6) have shown that subjects with a positive ASST generally have more numerous and widely distributed lesions, higher itch scores, frequent systemic symptoms, associated thyreopathies and lower levels of IgE than ASST-negative subjects, indicating that they present more severe clinical pictures than the ASST-negative subjects.

The present study was carried out on CIU subjects seen in our centre with the aim of distinguishing them as serum-positive or serum-negative to evidence the clinical differences. We also tried to find correlations between the presence of fully developed autoimmune disorders, such as thyreopathy, and atopy, in the two groups.

MATERIALS AND METHODS

Assessment was performed in a retrospective study of 68 Italian subjects (46 women, 22 men; age range 19–81 years) with established diagnosis of CIU. None of the subjects was undergoing treatment with steroids or cyclosporin A upon testing, and those who had been taking antihistamines were subjected to a 4-day wash-out before testing.

Physical urticaria, allergic urticaria (IgE-mediated), urticaria vasculitis, C_1-esterase inhibitor deficiency, drug or alcohol abuse, pregnancy and lactation were considered as exclusion criteria.

ASST was performed according to Greaves' method (2) in all 68 subjects, giving us two comparable main groups. Moreover, serum-evoked histamine release from basophils of healthy donors was used in ASST-positive and ASST-negative subjects.

Basophil histamine release assay (HRA)

Leukocyte suspensions were prepared from two normal non-atopic donors whose basophils were previously shown to release 30% of total histamine content on challenge with an optimal dose of anti-IgE. These cells were treated with 10 mM lactic acid (pH 3.9) to dissociate IgE. Seventy-five microlitres of patients' sera were incubated with 75 µl of leukocyte suspension for 40 min at 37°C. After incubation the supernatants were separated by centrifugation at 3000 g for 5 min at 4°C, and histamine release was measured by an automated fluorometric method. The results were expressed as percentage of histamine release (HR) and calculated as follows: % $HR = (A - B)/T \times 100$, where A = HRA-induced HR, B = basal HR, T = total content. A 5% release cut-off value was used.

Baseline investigations in all patients included the detection of circulating immuno-complexes (CIC), autoantibodies

 ISSN 0001-5555
DOI: 10.1080/00015550410026939

(ANA, anti-gastric parietal cells, anti-smooth muscle, anti-thyroglobulin, anti-peroxidase, anti-TSH receptor), anti-*Helicobacter pylori* antibodies, and thyroid function (fT_3, fT_4, TSH).

Specific clinical features recorded were the signs and symptoms observed during the last week before evaluation. Urticarial activity was evaluated according to the Breneman scale score, which includes number, duration and size of wheals, number of episodes, and itching severity (7). We also recorded the presence of angioedema, gastrointestinal symptoms and flushing. The possible co-existence of autoimmune thyreopathy and coeliac disease was accurately investigated. Finally, the subjects were also classified on the basis of family history of atopy and personal atopic symptoms (IgE > 100 KU/l, atopic dermatitis, asthma, hay fever and rhinitis).

Statistical analysis

The results for the two subgroups (positive versus negative ASST) were expressed as a percentage, and statistical significance ($p < 0.05$) was assessed by the χ^2 test.

RESULTS

Skin test, in vitro histamine release assay and clinical data

Twenty-three of the 68 (33%) subjects had a positive reaction to the skin test. The serum-positive group was composed of 14 women and 9 men (median age 45.5 years), while the 45 ASST-negative subjects were 32 women and 13 men (mean age 41 years). There was no significant difference in the age distribution of the two groups.

Sera from 18/68 (26.4%) CIU subjects released $\geq 5\%$ histamine from the basophils of healthy donors, and all these subjects were in the ASST-positive group (Table I). Also, subjects with positive ASST had significantly higher numbers of wheals than the ASST-negative subjects (Table I).

No differences were noticed in wheal distribution on the skin surfaces: in both groups the lesions were located predominantly on the trunk and limbs, whereas the face and neck were mostly spared. Wheals of the most recent episodes and those present at the time of observation showed identical shape and size in both subsets. All the lesions were smooth, oedematous, pink or red in colour, sometimes surrounded by a bright red flare, and ranged from a few millimetres to 2.5 cm in diameter.

Table I. *Distinguishing features of patients with chronic idiopathic urticaria in relation to outcome of autologous serum skin test (ASST)*

Clinical features*	ASST-pos. $n=23$ n (%)	ASST-neg. $n=45$ n (%)	p value
Positive HRA	18 (78.2)	0	<0.0001
No. of daily wheals			
≤ 20	7 (30.4)	36 (80)	
>20	16 (69.6)	9 (20)	<0.0001
No. of episodes in last week			
0–1	9 (39.1)	38 (84.4)	
≥ 2	14 (60.9)	7 (15.6)	<0.0001
Pruritus			
None–mild	5 (21.7)	32 (71.1)	
Moderate–severe	18 (78.3)	13 (28.9)	0.001

*referring to the week before questionnaire.
HRA, histamine release assay.

The overall frequency of urticaria episodes was greater in the ASST-positive group (Table I). According to the responses to the itch questionnaire, pruritus was severe in 52% and mild in 22% of the serum-positive subjects, compared with severe in 7% and mild in 58% of the subjects without antibodies. There was no significant difference between the subjects with and without antibodies in the incidence or distribution of angioedema, documented in 65% of serum-positive and 53% of serum-negative cases. Gastrointestinal symptoms and flushing had been experienced during urticarial episodes in 0–3 subjects in the two groups.

The different frequencies of autoimmune thyreopathies in the two groups (13% vs 2%) was not significantly different. One subject presented coexisting coeliac disease, chronic urticaria and positive ASST. Finally, seven serum-positive subjects (30%) referred personal or family history of atopic diseases, but a similar percentage finding was evidenced in the serum-negative group.

Serum immunopathological features

No differences could be detected between the two groups in either thyroid function abnormalities or incidence of antinuclear antibodies (ANA). Organ-specific autoantibodies (anti-thyreoglobulin, peroxidase, parietal gastric cells and smooth muscle) were found more frequently and were numerically more in the serum-positive subjects (11 vs 5 cases), but the difference was not statistically significant.

Anti-*H. pylori* IgG antibodies were increased in 2 of 9 (22%) subjects with antibodies and in 7 of 10 (70%) without antibodies. This finding was very close to significance, with $p=0.06$. Circulating immunocomplexes were not detected in any of the positive subjects.

DISCUSSION

The findings of our study clearly agreed with both the female predominance of the disease (8) as well as the percentages of serum-positive cases, repeatedly assessed by English and American investigators at 27–50% of CIU subjects (2).

Histamine release assay was positive in 26% of our sera, that is in the majority of the ASST-positive subjects, but not in all. This discrepancy has already been noted in previous studies (9) and it suggests that

the activity of autoantibodies could be more easily initiated *in vivo* than *in vitro*, where histamine-releasing co-factors (complement or others) may be absent or fail to have an effect. Moreover, it reflects the presence in our series of serum-positive subjects who experience urticaria less than once a week (Table I) and confirms that the occurrence of anti-FcεRI autoantibodies is independent of the state of disease activity (10). In fact, the detection of anti-FcεRI antibodies in subjects in remission and even in healthy subjects (11) further suggests that antibody functional activity may depend on the receptor being occupied by its natural ligand (12).

No significant differences could be found between subjects with and without antibodies with regard to mean age, sex, and clinical morphology of individual wheals, which closely reproduced the prototypic features of chronic urticaria. The size and distribution of the lesions could not be regarded as differential parameters restricted to the individual subgroups.

However, subjects with autoantibodies presented a more severe form of urticaria, by virtue of the higher number of lesions occurring simultaneously, the higher frequency of acute attacks during the week before the observation and finally the higher itch scores. All these investigations were statistically supported and do, indeed, represent a distinctive characteristic of subjects with chronic autoimmune urticaria, as previously reported (5).

Angioedema was recorded in 39 of our 68 subjects (57%), a moderately lower proportion than that reported by Sabroe et al. (5). A reasonable explanation for the difference might be the different selection of patients: the subjects in our series came directly from general practitioners, but those in Sabroe's study were referred by specialized centres due to the peculiar severity of the disease. In our series there were no significant differences between the serum-positive and serum-negative groups with regard to associated systemic symptoms and atopy frequency, which were just as common as previously documented (13).

Similarly, there was no difference in the Breneman's scores for the atopic and non-atopic subjects, although it was expected that the atopic subjects would belong mostly to a less severe disease subgroup. In fact, it has been demonstrated that the atopic subject's trend towards high levels of IgE can prevent the binding of anti-FcεRI antibodies to the receptor, already saturated by immunoglobulins (1). The apparent bias is most likely due to an insufficient number of subjects in the study.

The causative role of *H. pylori* in urticaria has been widely debated in recent years. Most observations (14, 15) suggest that *H. pylori* represents a link between autoimmunity in idiopathic urticaria and chronic infection because of possible development of pathogenic autoantibodies by molecular mimicry, perhaps against lipopolysaccharide in *H. pylori*. Our findings seem to disagree with these data, as ASST-negative subjects showed anti-*H. pylori* IgG antibodies ($p = 0.06$) more often than ASST-positive subjects.

REFERENCES

1. Grattan CHE, Francis DM, Hide M, Greaves MW. Detection of circulating histamine-releasing autoantibodies with functional properties of anti-IgE in chronic urticaria. Clin Exp Allergy 1991; 21: 695–704.
2. Greaves MW. Chronic urticaria. J Allergy Clin Immunol 2000; 105: 664–667.
3. Fiebiger E, Maurer D, Holub H, Reininger B, Hartmann G, Woisetschlager M, et al. Serum IgG autoantibodies directed against the alpha chain of FcεRI. A selective marker and pathogenetic factor for a distinct subset of chronic urticaria patients? J Clin Invest 1995; 96: 2606–2612.
4. Zweiman B, Valenzano M, Atkins PC, Tanus T, Getsy JA. Characteristics of histamine-releasing activity in patients with chronic idiopathic urticaria. J Allergy Clin Immunol 1996; 98: 89–98.
5. Sabroe RA, Seed PT, Stat C, Francis DM, Barr RM, Kozba Black A, et al. 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: 443–450.
6. 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.
7. Breneman D, Bronsky EA, Bruce S, Kalivas JT, Klein GL, Roth HL, et al. Cetirizine and astemizole therapy for chronic idiopathic urticaria: a double-blind, placebo-controlled, comparative trial. J Am Acad Dermatol 1995; 33: 192–198.
8. Sibbald RG, Cheema AS, Lozinski A, Tarlo S. Chronic urticaria: evaluation of the role of physical, immunologic and other contributory factors. Int J Dermatol 1991; 30: 381–386.
9. Asero R, Tedeschi A, Lorini M, Salimbeni R, Zanoletti T. Chronic urticaria: novel clinical and serological aspects. Clin Exp Allergy 2001; 31: 1105–1110.
10. Zuberbier T, Henz BM, Fiebiger E, Maurer D, Stingl G. Anti-FcεRI alpha serum autoantibodies in different subtypes of urticaria. Allergy 2000; 55: 951–954.
11. Horn MP, Gerster T, Ochsenberger B, Derer T, Kricek F, Jouvin MH, et al. Human anti-FcεRIalpha autoantibodies isolated from healthy donors cross-react with tetanus toxoid. Eur J Immunol 1999; 29: 1139–1148.
12. Horn MP, Pachlopnik JM, Vogel M, Dahinden M, Wurm F, Stadler M, et al. Conditional autoimmunity mediated by human natural anti-FcεRI alpha autoantibodies? FASEB J 2001; 15: 2268–2274.
13. Juhlin L. Recurrent urticaria: clinical investigation of 330 patients. Br J Dermatol 1981; 104: 369–381.
14. Gala Ortiz G, Cuevas Agustin M, Erias Martinez P, de la Hoz Caballer B, Fernandez Ordonez R, Hinojosa Macias M, et al. Chronic urticaria and *Helicobacter pylori*. Ann Allergy Asthma Immunol 2001; 86: 696–698.
15. Hizal M, Tuzun B, Wolf R, Tuzun Y. The relationship between *Helicobacter pylori* IgG antibody and autologous serum test in chronic urticaria. Int J Dermatol 2000; 39: 443–445.