

Reactivity to autologous serum skintest and clinical features in chronic idiopathic urticaria

E. Nettis, P. Dambra, L. D'Oronzio, E. Cavallo, M. P. Loria, M. Fanelli, A. Ferrannini and A. Tursi

Department of Medical Clinic, Immunology and Infectious Diseases, Division of Allergy and Clinical Immunology, Chair of Medical Statistics, University of Bari, Italy

Summary

The autologous-serum skin test (ASST) can cause a wheal-and-flare response in some cases of chronic idiopathic urticaria. We subjected 102 patients affected by chronic idiopathic urticaria to this test and studied some clinical parameters to detect any significant differences between ASST-positive and ASST-negative patients. The only significant difference we noted between the two groups was the incidence of angioedema ($P = 0.01$). We suggest that the ASST cannot be used alone either to predict the severity of urticaria or to define it as 'autoimmune'.

Report

The pathogenesis of chronic idiopathic urticaria (CIU) has not yet been fully elucidated and, despite a detailed history and extensive laboratory investigations, it is not usually possible to indicate any probable cause of the urticaria. Various studies have demonstrated IgG autoantibodies against IgE and/or Fc ϵ RI α in the serum of some patients with CIU.^{1, 2} Although their clinical significance is still unclear, Fc ϵ RI α autoantibodies have been demonstrated in about one-third of patients with chronic urticaria. Furthermore, in some cases of CIU intradermal injection of autologous serum can cause a wheal-and-flare response.³ The aim of our study was to verify if there were any significant clinical differences between patients with positive and with negative autologous-serum skin test (ASST).

We administered the ASST to 102 patients (80 female and 22 male) affected by CIU, defined as recurrent wheals occurring for more than 2 months and in which all possible causes of angioedema and urticaria had been excluded on the basis of the most useful diagnostic protocol.⁴ After an accurate history and physical

examination of each patient we determined the following parameters: complete blood count; erythrocyte sedimentation rate; C-reactive protein; assessment of hepatic function and renal function; exclusion of bacterial and/or viral focal and parasitic infections; level of thyroid hormones; C1-INH factor. When indicated, ray and pulse-echo diagnoses were made. To define an atopic diathesis, the skin prick test for common inhalant and food allergens (Bayer-DHS, Milan, Italy) and determination of specific serum IgE (CAP-System, Pharmacia, Milan, Italy) were carried out. In cases with a positive history, patch tests with the Italian Group of Environment and Contact Dermatitis Research (GIRDCA) standard series (Hermal-Trolab, Bracco, Milan, Italy) were performed according to International Contact Dermatitis Research Group recommendations. Patients with clinical evidence of urticarial vasculitis or physical urticaria, renal or hepatic disease, diabetes, hypertension, epilepsy or neoplasia were excluded.

The ASST was performed as follows. Fifty-microlitre aliquots of autologous serum, 0.9% sterile saline (negative control) and histamine (10 μ g/mL, positive control) were injected into the dermis of the volar aspect of the forearm. Wheal-and-flare responses were evaluated at 30 min and, where shown, reassessed at 60 min. The ASST response was taken to be positive when the serum-induced wheal had a diameter at least 1.5 mm greater than the saline-induced wheal.⁵ ASSTs were

Correspondence: E. Nettis, Cattedra di Allergologia e Immunologia Clinica, Padiglione Chini – Policlinico, Piazza Giulio Cesare, 70124 Bari, Italy. Tel.: +39 0805592281. Fax: +39 0805478780. E-mail: e.nettis@allergy.uniba.it

Accepted for publication 6 August 2001

performed by only two physicians to avoid interpersonal variation in performing and interpreting the test.

None of the patients was taking antihistamine, steroid or immunosuppressive drugs at the time of the investigation. The clinical details we noted were a personal or family history of atopy, the duration in months of the urticaria, the duration (greater than or less than 24 h) of individual urticarial wheals and their distribution, and any association with autoimmune or infectious diseases. Moreover the number and size of the wheals and severity of the itching were scored as follows: number of wheals, 0 = no wheals, 1 = 1–5, 2 = 6–15, 3 = >15; wheal size, 1 = <5 mm, 2 = 5–15 mm, 3 = >15 mm; itching, 0 = none, 1 = mild, 2 = moderate, 3 = severe. The χ^2 test was used to detect associations between positive ASST and clinical features using Yates's correction for continuity when necessary, and Student's *t* test for independent samples was used to test for significant differences of mean duration of the symptoms between ASST-positive and ASST-negative patients.

Serum from 42 of 102 subjects (41.2%) induced a wheal-and-flare response, without significant differences ($\chi^2 = 0.001$, $P = 0.977$) between female (41.25%) and male (40.91%) patients. There were 57 patients (55.9%) with a positive family history and 44 (43.1%) with a personal history of atopy. The ASST was positive

in 21 (36.84%) of the former and in 20 (45.45%) of the latter, showing no significant difference ($\chi^2 = 0.638$, $P = 0.425$). There was no significant difference between patients with and without response to ASST as to the duration of urticaria; in fact the mean duration of the symptoms was 8.47 and 7.82 months, respectively ($t = 0.35$, $P = 0.726$) (Table 1). The urticarial symptoms presented daily in the majority of subjects, with no significant difference ($\chi^2 = 0.251$, $P = 0.616$) between patients with positive and negative ASST (87.5% and 81.67%, respectively). The distribution of wheals was no different in the two groups (data not shown), nor was there any significant difference in the wheal number and size between patients with positive and negative ASST (Table 2). The itching scores were also similar in the two groups of patients, as shown in Table 2. The only significant difference we noted between the groups was the incidence of angioedema. In fact 29/42 (69.05%) patients with a positive ASST presented this symptom compared to 26/60 (43.33%) patients with a negative ASST ($\chi^2 = 6.575$, $P = 0.010$). Anti-thyroid autoantibodies were detectable in both groups, without any significant difference ($\chi^2 = 0.608$, $P = 0.436$) (Table 1) between subjects with and without reactivity to ASST (53.85% and 46.15%, respectively). The prevalence of helicobacter pylori antibodies, assayed in 36/102 patients, was higher in

Table 1 Some features of patients (102) and positive and negative ASST

	<i>n</i>	No. positive ASSTs patients (%)	No. negative ASSTs patients (%)
Male	22	9 (40.91%)	13 (59.09%)
Female	80	33 (41.25%)	47 (58.75%)
Patients with family history of atopy	57	21 (36.84%)	36 (63.16%)
Patients with personal history of atopy	44	20 (45.45%)	24 (54.55%)
Patients with antithyroid autoantibodies	13	7 (53.85%)	6 (46.15%)
Mean duration in months of urticaria		8.47	7.82

Table 2 Scores for urticaria symptoms: distribution and percentage of patients with positive and negative ASST

		Score				Statistical significance
		0	1	2	3	
Wheal number						
Positive ASST	–		0%	71.43%	28.57%	$\chi^2 = 2.26, P = 0.323$
Negative ASST	–		3.33%	76.67%	20%	
Wheal size						
Positive ASST	–		0%	56.52%	43.48%	$\chi^2 = 3.24, P = 0.198$
Negative ASST	–		12.9%	51.61%	35.48%	
Itching						
Positive ASST	0%	0%		19.05%	80.95%	$\chi^2 = 2.36, P = 0.5$
Negative ASST	1.67%	1.67%		11.67%	85%	

the group with negative response to ASST (43.48%) compared to patients with positive ASST (23.08%), even if this result was again not statistically significant ($\chi^2 = 0.745$, $P = 0.338$).

Discussion

The proportion of patients with a positive response to the ASST in our study confirms other authors' data. However, we noted that the majority of parameters we examined to define the severity of urticaria showed no significant difference between patients with a wheal-and-flare response to ASST and patients with a negative response, in contrast with previous studies. Only the incidence of angioedema was significantly different in the two groups, but this is not sufficient to indicate that patients with a positive ASST had more severe urticaria. So we believe that the ASST cannot be used alone to predict the severity of urticaria. Moreover a positive response to the ASST is not sufficient to define the urticaria as 'autoimmune'.^{4, 5} In fact, recent findings demonstrate that skin reactivity to ASST may not be due to IgG autoantibodies against IgE and/or FcεRIα.⁶ Although anti-FcεRIα are mostly found in chronic urticaria, they are also detectable both in patients affected by other diseases and in normal subjects.⁷ Furthermore, these autoantibodies are found in patients with nonidiopathic urticaria after treatment of the identified causes and remission of the disease.⁸ Therefore we suggest more critical use of the ASST in patients with CIU. Above all, it cannot be excluded that individual factors and/or the chronic inflammatory process could induce the production of autoantibodies. In this case, even if their detection suggests that an autoimmune process is in progress, it is not enough to explain the pathogenesis of urticarial forms due to yet unidentified mechanisms. Such

mechanisms could be responsible for a positive response to the ASST, through the release of unknown factors in the patient's sera. Further studies are required to discover these factors other than autoantibodies and to gain a better understanding of the pathogenesis of CIU.

References

- 1 Hide M, Francis DM, Grattan CEH *et al.* Autoantibodies against the high affinity IgE receptor as a cause of histamine release in chronic urticaria. *N Engl J Med* 1993; **328**: 1599–1604.
- 2 Fiebiger E, Maurer D, Holub H *et al.* Serum IgG autoantibodies directed against the α chain of FcεRI: a selective marker and pathogenetic factor for a distinct subset of chronic urticaria patients? *J Clin Invest* 1995; **96**: 2606–12.
- 3 Niimi N, Francis DM, Kermani F *et al.* Dermal mast cell activation by autoantibodies against the high affinity IgE receptor in chronic urticaria. *J Invest Dermatol* 1996; **106**: 1001–6.
- 4 Henz BM, Zuberbier T, Grabbe J, Monroe E, eds. *Urticaria – Clinical, Diagnostic and Therapeutic Aspects*. Berlin: Springer Verlag, 1997.
- 5 Sabroe RA, Grattan CE, Francis DM *et al.* The autologous serum skin test: a screening test for autoantibodies in chronic idiopathic urticaria. *Br J Dermatol* 1999; **140**: 446–52.
- 6 Fagiolo U, Kricek F, Ruf C *et al.* Effects of complement inactivation and IgG depletion on skin reactivity to autologous serum in chronic idiopathic urticaria. *J Allergy Clin Immunol* 2000; **106**: 567–72.
- 7 Marone G, Spadaro G, Palumbo C *et al.* The anti-IgE/anti-FcεRIα autoantibody network in allergic and autoimmune diseases. *Clin Exp Allergy* 1999; **29**: 17–27.
- 8 Zuberbier T, Henz BM, Fiebiger E *et al.* Anti-FcεRIα serum autoantibodies in different subtypes of urticaria. *Allergy* 2000; **55**: 951–4.