Original Article

Autologous Serum and Plasma Skin Tests in Chronic Spontaneous Urticaria: A Reappraisal

Abstract

Aim: The objective of this study was to assess autologous serum skin test (ASST) vs autologous plasma skin test (APST) response in chronic spontaneous urticaria (CSU) patients and study the significance of intensity of positive responses in relation to clinicoepidemiological parameters. **Materials and Methods:** One hundred CSU patients and 100 age and sex-matched controls were recruited. The demographic and clinical features were recorded in all patients and routine investigations were performed. ASST and APST tests were performed as per the standard guidelines. **Results:** The mean duration of illness was 4.85 ± 5.07 years, 90% patients were APST (+), 68% ASST (+), and 22 patients were only APST (+). Positive predictive value (PPV) of ASST and APST was 90.7% and 95.7%, respectively. A significant inverse association was seen between thyroid status and serum IgE levels with APST and ASST positivity. **Conclusion:** APST appears to have better PPV and high intensity of positive response on autologous tests, and correlates with ANA positivity and angioedema.

Keywords: *Autoimmune, autologous plasma skin test, autologous serum skin test, chronic sponataneous urticaria*

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Introduction

Chronic spontaneous urticaria (CSU) is a common disorder with a complicated, incompletely fathomed etiopathogenesis. CSU is defined as daily or almost daily occurrence of wheals for at least 6 weeks with or without angioedema. It is commonly reported between 4th and 6th decades of life with a female preponderance.[1] Despite the availability of a broad panel of diagnostic tests, identification of specific causative factor in CSU remains elusive.

Circulating mast cell-activating agents have been identified in blood of CSU patients; a subgroup of these patients has autoantibodies directed against the IgE receptor FcεRI or against IgE that functions as mast cell-activating signals. These autoantibodies have been shown to activate blood basophils and cutaneous mast cells *in vitro*. The presence of these autoantibodies may be clinically important in a group of severely affected, treatment-resistant patients, where immunomodulatory treatments may be valuable. Patients with autoantibodies have no distinctive diagnostic clinical features. Autoimmune and non-autoimmune cases are indistinguishable clinically and histologically. However, they do tend to have more severe urticaria.[2-13]

Autologous serum skin test (ASST) is a simple *in-vivo* clinical test for the detection of basophil histamine-releasing activity. Sabroe *et al*. found that ASST has a sensitivity of approximately 70% and a specificity of 80%, and it may be used as a reasonably predictive clinical test to indicate the presence of functional circulating autoantibodies.[14] A positive ASST has been associated with prolonged disease that is poorly responsive to routine therapy. One important advantage of testing is to promote a more tailored prognostic counseling and earlier use of immunosuppressive drugs.[14] Studies have also demonstrated a significant relation between chronic idiopathic urticaria (CIU) diagnosed by ASST and clinical parameters like frequency of attacks, duration of individual episodes, duration of wheals, regional involvement, and being less responsive to conventional antihistamine therapy.[15,16] Albeit ASST is commonly used *in vivo* validated test, which is positive in

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30–67% of patients in CSU,[14,17] concerns have been raised regarding its interpretation and specificity.

The basophil histamine release assay is currently the gold standard for detecting functional autoantibodies in the serum of patients with chronic urticaria. However, this bioassay is difficult to standardize because it requires fresh basophils from healthy donors and it is also time consuming, hence it remains restricted to scientific research. Hence, ASST is considered to be a bedside clinical test that can detect the presence of autoimmunity in patients with CIU. Depending on the method of antibody detection, various studies have reported that the prevalence of ASST positivity in patients of chronic urticaria varies from 35% to 58%.[16]

Asero *et al*. have reported that the autologous plasma skin test (APST) is more sensitive than ASST, but cannot be considered as a screening test for histamine-releasing autoantibodies.[18] The prevalence of ASST positivity ranges from 42% to 68% whereas the prevalence of APST positivity varies from 14% to 97%. APST generates more positive responses than ASST because plasma contains coagulation factors and complements, which are consumed in the formation of clots in ASST, and hence, less positive results are seen.[19] The demonstration of autoantibodies in only some patients with positive ASST and APST (25–50%) confirms that there are factors other than autoantibodies that play a role in the etiology of urticaria.

Although the literature includes various results, these variations depend on multiple factors, including methods of skin test, interpretation criteria of skin test results, type of anticoagulant, centrifuging blood specimen, and methods of serum separation. For example Asero *et al*. used ethylenediaminetetraacetic acid (EDTA) as an anticoagulant, and hence the positive results reported to be 97% of the cases.[17,18] All relevant studies so far have reported that both the APST and ASST can be used for diagnostic purposes in patients with chronic autoimmune urticaria (CAU).[16,20] Which of these is more sensitive and whether or not their positivity correlates with the disease severity, varies between different studies and cannot be decisively concluded.

Although many studies have assessed these two investigations individually, there is scarcity of studies that have compared the two, and to our knowledge, no study has investigated the significance of responses in both these tests. Hence, we wanted to compare the results of ASST and APST in patients with CSU and correlated the intensity of response with various clinicoepidemiological parameters.

Materials and Methods

All patients of chronic urticaria attending the urticaria clinic at our institute were screened for 1 year; 150 chronic urticaria patients, aged >18 years, having a disease duration longer than 6 months were enrolled. CSU was defined as patients suffering from urticaria for more than 6 weeks duration. Those with a history of physical urticaria and pregnant and lactating women were excluded from the study; 100 age and sex-matched healthy controls were also studied to observe the distribution of ASST, APST, serum IgE levels, and thyroid profile among general population. The study was approved by the Institutional Ethics Committee, and a written informed consent was obtained from all patients and volunteers.

Medical history and physical examination was noted on a predesigned proforma. Laboratory investigations including complete blood count, metabolic panel, urine and stool analysis, serum IgE levels, ANA, and thyroid function tests (TFTs) were performed.

ASST and APST tests were performed as per standard guidelines.[16,20] Patients were advised to stop antihistamines, doxepin, and steroids 2 days, 1 week, and 3 weeks prior to the test, respectively.

To obtain serum, venous blood (3 ml) was taken in a sterile glass tube without clotting accelerator and allowed to clot at room temperature for 30 minutes. Serum was separated by centrifugation at 500 g for 15 minutes.

To obtain plasma, 4 ml of venous blood was collected in a sterile vacutainer containing 0.5 ml of 0.105 mol/l sodium citrate. These samples were kept at room temperature for 15 minutes, and then centrifuged for 3 min at 1250 g to obtain plasma.

Histamine diphosphate 10 μg/ml and sterile physiological saline (0.9%) were used as positive and negative controls, respectively.

Fifty microlitres (two units of 40 units/1 ml insulin syringe) of each autologous plasma, serum, sterile physiological saline, and histamine were injected intradermally into the volar aspect of the left forearm keeping a gap of 3–5 cm. Areas known to be involved in whealing in previous 24 hours were avoided. Strict aseptic precautions were followed.

Wheal diameter was recorded at 30 minutes as the average of two maximum perpendicular diameters measured with the help of a measuring scale. ASST and APST were considered to be positive if the wheal induced by serum or plasma, respectively, was >2 mm in diameter than that induced by saline. The intensity of this positive response was graded arbitrarily:

- + (low intensity) = ≤3 mm with no peripheral surrounding erythema
- 2+ (moderate intensity) = 4–6 mm with mild peripheral erythema
- 3+ (high intensity) = >6 mm with bright red peripheral erythema.

Statistical analysis

For interpretation of the results, descriptive statistical methods (mean, standard deviation) as well as unpaired

t-test for comparison of groups, Chi-square test, and odds ratio for comparing quantitative data were performed.

Results

Among 150 CSU patients screened, 100 were eligible, of which 48 were males and 52 were females (M:F = 1:1.08), with a mean age of 34.95 ± 11.96 years (mean age of females: 35.97 years; mean age of males: 33.35 years). The mean duration of illness was 4.85 ± 5.07 years. More than half of the study cohort had experienced >2 episodes of urticaria; 65% patients had only urticaria and remaining had urticaria with angioedema.

Autologous serum skin test vs autologous plasma skin test

On examining the response to autologous tests, among 100 patients, 68 were ASST (+) and 90 were APST (+). All ASST (+) patients were also positive for APST, and remaining 22 were only APST (+). The patients who were only APST (+) demonstrated a female predominance (F:18, M:4), <30 years of age, a refractory/resistant disease, and longer duration of disease (63.6% of them requiring immunosuppressive treatment methotrexate or cyclosporine in the past and the remaining patients required more than one antihistamines for disease controls). Those with only ASST (+) and both the autologous tests positive did not have any significant clinicoepidemiological details. Among controls, only 8% and 4% were found to be ASST (+) and APST (+), respectively. Comparison between the cohorts and controls for ASST/APST positivity was statistically significant, which was higher in patient population than controls (P < 001). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) are summarized in Table 1.

Intensity of response analysis

The positive response on ASST and APST were further assessed for the intensity of response obtained; it was observed that in APST 63, 11, and 16 patients and in ASST 48, 16, and 14 patients had + (low), ++ (moderate) and +++ (high) positive response, respectively [Table 2]. Those with severe response (3+) complained of increased itching followed by burning sensation at the tested site, especially in patients with APST (+).

Additional features observed were:

- 3+ or high intensity response on ASST and APST was seen in 6/16 (37.5%) patients with angioedema who had respiratory difficulty during eruption (1 patient required hospital admission once)
- ANA was positive in 10 patients, 60% of them demonstrated 3+ or high intensity response on both ASST and APST; on further investigations, 4/6 patients also had dsDNA antibody positive along with low C3 and C4 complement levels, however, none manifested any signs and symptoms of collagen vascular disorder.

Table 1: Senstivity and specificity of ASST and APST on comparing cases with controls

Test	Sensitivity	Specificity	Positive predictive value	Negative predictive value
ASST	78%	92%	90.7%	80.7%
APST	90%	96%	95.7%	90.5%

Table 2: Positive response grading in ASST and APST

	APST	ASST
Mild	63	48
Moderate	11	16
Severe	16	14

Sixteen patients demonstrated TFTs abnormalities, hypothyroidism (n = 15), and hyperthyroidism (n = 1). Hypothyroidism was encountered more in females (P < 0.01). Thyroid autoantibodies were seen in 13% of patients and 4% of controls. The distribution of anti-TPO antibodies among females and males, patients, and controls did not show any statistically significant variation. A significant inverse association was observed between TFTs and APST as 92.9% of those with normal TFTs were APST (+), ($\kappa = -0.062$ $P = 0.029$).

IgE levels were found to be raised in only 9% patients; they all had a positive family history for atopy (asthma in 6, allergic rhinitis in 3). The serum levels of IgE varied from 500 IU to 1200 IU; 8/9 (88.9%) patients demonstrated a moderate positive response only on APST. A significant inverse correlation was noted between IgE levels and ASST (+) as 84% of those with normal IgE levels were ASST (+) ($\kappa = -0.141$ $P = 0.012$).

The mean urticaria activity score (UAS) among all CSU patients was (4.2 ± 1.24); these scores did not significantly correlate with the intensity of positive response on either ASST or APST. Correlation between the intensity of positive response on autologous skin tests with regards to gender, duration of disease, and thyroid status of the study cohort did not bear any significance.

Discussion

Research is still underway to expound the enigmatic pathogenesis of CSU. Recent studies have incriminated platelets to play a vital role in various immune and inflammatory disorders such as allergic dermatitis (atopic dermatitis), psoriasis, urticaria, and inflammatory bowel disease.[21]

Platelet activation factor-4 stimulates histamine release from rat mast cells. Cutaneous reaction following the intradermal injection of autologous serum and plasma in ASST and APST reflects autoreactivity in patients with chronic urticaria. ASST is a test for autoreactivity rather than a specific test for autoimmune urticaria with only moderate

specificity as a marker for functional autoantibodies against IgE or the high affinity IgE receptor (FcεRI), detected by the basophil histamine release assay, however, with a high negative predictive value for CSU patients without them.[21]

The extrinsic pathway of clotting cascade is involved in the pathogenesis of CSU and the disease severity is associated with the activation of coagulation cascade.[16,22-24] There are recent reports of APST to be more sensitive than ASST,[16] thus it is predictable that APST generates more positive responses than ASST because plasma contains coagulation factors and complements.[25-27]

The prevalence of APST positivity varies between 14% and 97% whereas that of ASST positivity ranges from 42% to 68%.[16,28,29] In our study, the positive prevalence of autologous tests was 78% for ASST and 90% for APST, which is comparatively higher than most of the studies so far. Kocatürk *et al*.,[20] found that the specificity of ASST and APST was similar, whereas ASST was found to be more sensitive than APST in discriminating between CSU patients and controls. However, in our study we found APST to be more sensitive and specific than ASST with a higher positive predictive value, although it was not statistically significant. Twenty two patients in our study were positive only for APST and not *vice versa*; further analysis of these patients demonstrated a female preponderance, <30 years of age, longer disease duration, and resistant urticaria which was not improving with antihistamines with 63.6% of them requiring immunosuppressive treatment (methotrexate or cyclosporine).

False negative and positive results with ASST have been proposed owing to high amount of bradykinin generated during coagulation cascade leading to the release of proteinase enzymes that destroy C5a and the formation vasoactive mediators while the serum is being prepared leads to false positive results.[23,24] Asero *et al*. described APST and suggested it to be more sensitive than ASST,[18] which has been refuted by few researchers, claiming the higher rate of APST positivity in earlier studies being attributed to the failure to use negative control tests.[20,28-34] In our study, we found no significant correlations between ASST and APST positivity with respect to gender, disease duration, and personal or family history of atopy, which coincides with the findings of previous studies.[28,30]

We wanted to observe if there was any significance of the intensity of response during autologous skin tests in urticaria with regards to various clinico-epidemiological characteristics of patients. In the absence of any previous studies dealing with the intensity of positive response, we cannot compare our findings.

In our patients, an associated presence of angioedema demonstrated no significant correlation with ASST and APST outcome, as in earlier studies,[21,31,35-40] however, on assessing the intensity of positive response, 37.5% patients with severe angioedema demonstrated a high intensity response.

An increased prevalence of antithyroid autoantibodies among CSU patients have been cited by many researchers with prevalence ranging between 0 and 5.6%.[6-9,41,42] We found thyroid autoantibodies in 13% and 4% of our patients and controls respectively, which was not statistically significant. However, a statistically significant inverse association was noted between TFTs and APST; 92.9% of patients who were APST (+) had normal T_3 and T_4, TSH and anti TPO values ($P = 0.029$).

The relationship between atopy and chronic urticaria has been suggested by some authors, although some studies have observed no correlation between the two.[43-45] Only 9 patients in our study provided a family history of atopy and not in the patient *per se*. All of them were found to have increased IgE levels, and 84% of patients with normal IgE levels were ASST (+) ($P < 0.05$).

ANA positivity was seen in 10 patients; 6/10 demonstrated 3+ or high intensity positive response on ASST and APST. Four out of these 6 patients had low complement (C3 and C4) levels and dsDNA positivity. Thus, a high intensity of response on autologous tests could signify a presence of underlying ANA positivity, in which case the patient needs to be followed up, along with monitoring for collagen vascular disorder. Since there are no studies assessing the intensity of positive response on autologous blood tests in CSU, we are unable to compare our preliminary results.

Conclusion

Our study exemplifies that APST is probably better than ASST in identifying autoreactivity in CSU owing to better PPV and the presence of high intensity response on ASST/APST, which could signify the presence of an underlying ANA positivity or a severe angioedema, as noted in our study. Additional studies are required to further clear the enigma between APST and ASST and confirm and augment our various preliminary findings.

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Conflicts of interest

There are no conflicts of interest.

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