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Correlation of clinical features with positive autologous serum skin test in chronic urticaria

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Abstract
Recent reports have indicated the presence of autoantibodies in about one-third of patients with chronic urticaria and autologous serum skin test (ASST) is a simple and useful clinical test to demonstrate them. Our study aimed to find the proportion of patients with chronic urticaria having autoantibodies in their sera using autologous serum skin test (ASST) and to compare the clinical features of patients with positive and negative ASST. Study patients were subjected to ASST and their disease activity was measured using urticaria activity score(UAS). Statistical analysis was done using Chi-square test and Mann-Whitney test. Among the patients studied , autoantibodies were detected by ASST in the sera of 33.33% of patients with chronic urticaria and these patients had more prolonged duration of disease, high urticaria activity scores as well as increased serum IgE and absolute eosinophil counts.

Keywords: Autologous serum skin test, chronic urticaria, autoimmune urticaria

Introduction
Chronic urticaria (CU) is defined as wide spread short lived (<24 hr) wheals occurring daily or almost daily for atleast six weeks duration [1]. Clinically it manifests as wheals usually associated with itching. Associated systemic symptoms include malaise, headache, abdominal pain, arthralgia, dizziness, syncope or even anaphylaxis. Urticaria and angioedema may coexist in 50% of cases.
Mast cell degranulation is of central importance in the pathogenesis of CU [2, 3]. Studies have indicated the presence of autoantibodies in about one-third of patients with CU [4]. These histamine releasing autoantibodies are directed against either the subunit of the high affinity IgE receptor or IgE [5]. Patients with autoantibodies in their sera have no distinctive diagnostic clinical features though they do tend to have more severe and unremitting urticaria.
Basophil histamine release assay is currently the gold standard for detecting these functional autoantibodies in serum of patients with chronic urticaria [6]. However, this bioassay is difficult to standardize because it requires fresh basophils from healthy donors, is time consuming and it remains confined to research centers.
Autologous serum skin test (ASST) is the simple clinical test for the detection of basophil histamine- releasing activity [4, 6]. In India, ASST positivity was found to be 26.67% in chronic urticarial [7]. ASST has a sensitivity of approximately 70% and a specificity of 80% when read as a pink serum induced wheal, 1.5 mm or greater than adjacent normal saline control injection, at 30 minutes and can be used as a reliable clinical test to indicate the presence of functional circulating autoantibodies [8].
Diagnosis of autoimmune urticaria is suspected in patients with severe presentations of chronic urticaria having a positive ASST. These patients are generally not very responsive to usual medications but shows remarkable improvement following plasmapheresis in some patients, highlighting the role of autoantibodies. Other treatment options include systemic corticosteroids and immunomodulatory agents such as cyclosporine and IV immunoglobulin [9].

Methodology
Patients with chronic urticaria, attending the outpatient department of Dermatology, Venereology and Leprology at ACME, Pariyaram (currently GMC, Kannur) were enrolled for the study during a period of one year.

Inclusion Criteria

- All patients attending the out patient department of Dermatology, Venereology and Leprology, with recurrent urticarial wheals of more than 6 weeks duration.
- Age 12 years and above.

Exclusion Criteria

- All patients on antihistamines for a period of 3 days prior to this test.
- Patients on any immunosuppressive drugs 6 weeks prior to this test.
- Patients with history of physical urticaria other than simple dermographism.
- Patients with urticarial vasculitis.
- Patients with known type I hypersensitivity reactions
- Pregnant females

Method of data collection

Informed consent was taken from all patients. Clinical details were recorded using a standard proforma. All patients were subjected to laboratory investigations included complete blood count, urine microscopic examination and other specific investigations if indicated. Absolute eosinophil count and serum IgE were done in all patients. Clinical symptoms and signs were graded on the basis of the modified urticaria activity score (UAS) which combines severity of itching and wheal number. Statistical analysis was done using Chi-square test for categorical variables and the nonparametric test (Mann-Whitney test) for other variables. A p-value of less than 0.05 was considered significant.

Procedure of ASST

2 ml of venous blood was collected in a sterile vacutainer and allowed to clot at room temperature for 30 minutes. Blood was sent to clinical laboratory for centrifugation at 2000 rpm for 15 minutes and the serum separated. Samples of 0.05ml (equivalent to 2 units on insulin syringe that has lml marked as 40 units) of autologous serum, and 0.9% sterile normal saline were separately injected intradermally into volar aspect of left and right forearm respectively. Wheal, redness and flare response was measured at 30 minutes. ASST was considered positive if the serum induced wheal has a diameter of > 1.5 mm than the saline induced response at 30 minutes.

Results

Of the 60 patients studied, 73.1% percent of patients who had duration more than one year had ASST positivity, which was found to be statistically significant. No statistical significance difference in the ASST negative and positive groups was found regarding the co-existence of angioedema or time of appearance of lesions.

Table 1: Association between Wheal Score and ASST

Wheal Score	ASST Negative		ASST Positive		P
	Count	Percent	Count	Percent	
< 10 wheals	22	100.0	0	0.0	<0.001
10 - 50 wheals	18	60.0	12	40.0	
50 wheals		0.0	7	100.0	
Involving almost the whole body	0	0.0	1	100.0	

Table 2: Association between Urticaria Activity Score and ASST

Urticaria Activity Score	ASST Negative		ASST Positive		P value
	Count	Percent	Count	Percent	
2 — 4	39	100.0	0	0.0	<0.001
5 — 7	1	4.8	20	95.2	

Table 3: Association between Absolute Eosinophil Count and ASST

Absolute Eosinophil Count	Negative		Positive		P value
	Count	Percent	Count	Percent	
Normal	32	86.5	5	13.5	<0.001
Increased	8	34.8	15	65.2	

Table 4: Association between Serum IgE and ASST

Serum IgE	ASST Negative		ASST Positive		P value
	Count	Percent	Count	Percent	
Normal	32	91.4	3	8.6	<0.001
Increased	8	32.0	17	68.0	

Discussion

The present study found that the percentage of patients with chronic urticaria who showed a positive reaction to ASST was 33.33%, which is comparable with earlier reports. Study by Sabroe *et al.* [10] found functional autoantibodies in 31% of 107 patients with chronic urticaria whereas Zweiman *et al.* [11] found it in 30% of 70 chronic urticaria sera while Tong *et al.* [12] found that serum from 52% of 50 chronic urticaria patients released histamine from basophils. In Mamatha *et al.* study, 34% of 100 chronic idiopathic urticaria patients had positive ASST [4]. The prevalence difference according to the ethnic group of population suggests a genetic background for the disease.

The mean duration of disease among patients with ASST positivity in the present study was found to be ≥ 1year, which was statistically significant and similar correlation was found in a study conducted by Sabroe *et al.* [13] As in a similar study done by Sabroe *et al.* [3] and Mamatha *et al.* [4]

our study also did not show any significant differences between ASST positive or negative patients regarding the association with angioedema. ASST positive patients had significantly more systemic symptoms in a study by Juhlin [14]. In particular gastrointestinal symptoms and flushing occur more frequently in patients with autoantibodies. Our study failed to reveal such associations.

Severity of urticaria, as measured by UAS (urticaria activity score = pruritus score + wheal score), was significantly higher in ASST positive group compared to ASST negative group. Study by both Sabroe *et al*. [15] and Caproni *et al*. [16] found more severe clinical presentation in those with positive ASST.

Abnormal TFT values were detected in two out of twenty ASST positive patients. The association of chronic urticaria with thyroid autoimmunity has been studied by Leznoff *et al*. [17] and it has been postulated that thyroid autoimmunity may play a role in the pathogenesis of chronic urticaria and angioedema. However, in contrast to previous studies [17], we did not find any difference in the incidence of thyroid disease. This is probably because an insufficient number of patients was included for the study of a disease of low incidence (thyroid autoimmunity) or because TFT and thyroid autoantibodies were not routinely measured for all patients.

The blood absolute eosinophil count (AEC) was significantly higher in ASST positive group than in ASST negative group. The role of tissue eosinophilia is unclear, but it is possible that release of toxic eosinophil major basic and eosinophil cationic proteins further augments histamine release from mast cells in the late phase of urticarial wheal.

Serum IgE level was significantly higher in ASST positive group compared to ASST negative group. The elevated levels of IgE may lead to over expression of IgE receptor FcεR1α which will bind to IgG autoantibodies. The study conducted by Azim *et al*. showed improvement in 7 of 12 patients having chronic autoimmune urticaria by anti-IgE, omalizumab which selectively binds to IgE [3]. Kaplan *et al*. postulated that omalizumab by decreasing the circulating IgE level, will in turn decrease IgE receptor density on basophils and cutaneous mast cells, thereby preventing activation by autoantibodies [18].

Conclusions

To conclude, autoantibodies detected by ASST were seen in the sera of 33.33% of patients with chronic urticaria and these patients had more prolonged duration of disease, high urticaria activity scores and raised serum IgE levels and absolute eosinophil counts .ASST is the only reliable test for the diagnosis of autoimmune urticaria which is simple, inexpensive and can be easily done in our clinical settings. The test is especially important from the therapeutic point of view as it helps us to decide regarding immunosuppressive therapy in such patients.

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