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Correlation of clinical features with positive autologous serum skin test in Urticaria

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Abstract
Autologous serum skin test (ASST) is the simplest and the best in vivo clinical test for the detection of basophil histamine- releasing activity. In India, ASST positivity was found to be 26.67% in chronic Urticaria. The details enquired from the patients include duration of disease, duration of individual wheals, frequency of attacks, distribution of wheals, associated systemic symptoms, provoking physical factors, food and drug intolerance, seasonal variation, associated angioedema. Out of total 60 patients, 38 patients gave history of exacerbation of symptoms during evening time. But there was no statistical correlation with ASST positivity. Out of total 60 patients 25 patients were found to have increased serum IgE values, of which 17 (68%) were ASST positive, found to be statistically significant.

Keywords: Autologous Serum Skin Test, Chronic Urticarial, Angioedema

Introduction
Chronic Urticaria {CU) is defined as wide spread short lived (<24hr) wheals occurring daily or almost daily for at least 6 weeks duration. CU is extremely disabling in its severe thrill and can be difficult to treat. Clinically it manifests as wheals usually associated with itching. Wheals may vary in size, shape, number, time of onset and duration: resolves without any pigmentation. Associated systemic symptoms include malaise, head ache, abdominal pain, diarrhea, arthralgia, dizziness, syncope or even anaphylaxis Urticaria and angioedema may coexist in 50% of cases [1].

Mast cell degranulation is of central importance in the pathogenesis of CU. Recent reports have indicated the presence of autoantibodies in about one-third of patients with CLT. These histamine releasing autoantibodies are directed against either the subunit of the high affinity IgE receptor or IgE. Patients with autoantibodies in their sera have no distinctive diagnostic clinical features though they do tend to have more severe and unremitting Urticaria [2].

Basophil histamine release assay is currently the 'gold standard for detecting, these functional autoantibodies in serum of patients with chronic urticarial. 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. Western blot, ELISA and flow cytometry may be useful for screening in the future, but it needs to be validated [3].

Autologous serum skin test (ASST) is the simplest and the best in vivo clinical test for the detection of basophil histamine- releasing activity. In India, ASST positivity was found to be 26.67% in chronic Urticaria. 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 reasonably predictive clinical test to indicate the presence of functional circulating autoantibodies [4].

Diagnosis of autoimmune Urticaria hinges mainly on clinical suspicion in patients with most severe presentations of chronic Urticaria along with a positive ASST. These patients are generally unresponsive to conventional therapy but remarkable improvement has been seen following plasmapheresis in some patients, thus highlighting the importance of autoantibodies. Other treatment options include systemic corticosteroids and immunomodulatory agents such as cyclosporine and IV immunoglobulin [5, 6].

Methodology

Patients with chronic Urticaria, attending the out patient department of Dermatology, Venereology and Leprology 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, ACME, Pariyaram 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 of all patients were recorded using a standard proforma.

The details enquired from the patients include duration of disease, duration of individual wheals, frequency of attacks, distribution of wheals, associated systemic symptoms, provoking physical factors, food and drug intolerance, seasonal variation, associated angioedema.

To rule out systemic causes of Urticaria, all patients were subjected to laboratory investigations included complete blood count, urine microscopic examination and other specific investigations if indicated. Clinical symptoms and signs were graded on the basis of the modified Urticaria activity score (ETAS) which combines severity of itching and wheal number.

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. Positive ASST was defined as serum induced wheal which has a diameter of > 1.5 mm than saline induced response at 30 minutes.

Results

Table1: Association between Wheal Score and ASST

Wheal Score	ASST Negative		ASST Positive		X2	P
	Count	Percent	Count	Percent		
< 10 wheals	22	100.0	0	0.0	27.6**	<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		

Here a significant correlation of increase in wheal score with ASST positivity was observed

Table 2: Association between Urticaria Activity 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	

Patients with ASST positivity have high UAS (>5), which was statistically significant

Table 3: Association between Angioedema and ASST

Angioedema	ASST Negative		ASST Positive	
	Count	Percent	Count	Percent
No	34	69.4	15	30.6
Yes	6	54.5	5	45.5

There is no significant correlation with angioedema and patients with ASST positivity

Table 4: Association between Time of the day when symptoms most severe and ASST

Time of the day when symptoms most severe	ASST Negative		ASST Positive	
	Count	Percent	Count	Percent
Early Morning	7	77.8	2	22.2
Day Time	7	53.8	6	46.2
Evening	26	68.4	12	31.6

Out of total 60 patients, 38 patients gave history of exacerbation of symptoms during evening time. But there was no statistical correlation with ASST positivity

Table 5: Association between Absolute Eosinophil Count and ASST

Absolute Eosinophil Count	Negative		Positive		X^2	P value
	Count	Percent	Count	Percent		
Present	32	86.5	5	13.5 17.06**		<0.001
Increased	8	34.8	15	65.2		

Out of total 60 patients 23 patients showed increased AEC, of which 15 (65.2%) were ASST positive, which was statistically significant

Table 6: Association between Serum IgE and ASST

Serum IgE	ASST Negative		ASST Positive		X2	P value
	Count	Percent	Count	Percent		
Present	32	91.4	-3	8.6	23.18**	<0.001
Increased	8	32.0	17	68.0		

Out of total 60 patients 25 patients were found to have increased serum IgE values, of which 17 (68%) were ASST positive, found to be statistically significant

Discussion

In our study, we used various parameters such as diurnal variations, family history of autoimmunity, seasonal variations, associations with medical conditions, drugs and all these Parameters did not have any significance in the study. These findings were similar to a study done by George, *et al*. and Mamatha, *et al.* Out of total 60 patients only 4 patients had Dermographism and there was no statistical correlation observed with ASST positivity.

Dermographic subjects comprise a special group. They do not have autoantibodies according to in vitro tests but manipulation of skin while injecting the sample may cause a wheal and flare response regardless of the substance injected and may be taken as false positive responses.

ASST positive patients had significantly more systemic symptoms in a study by In particular gastrointestinal symptoms and flushing occur more frequently Juhlin in patients with autoantibodies. Our study failed to reveal such associations.

Autoimmune diseases like thyroid disease, vitiligo, diabetes mellitus, pernicious anemia and rheumatoid arthritis were reported more commonly in patients with autoimmune Urticaria.

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. Both Sabroe, *et al*. and Caproni, *et al.* also found that patients with positive ASST presented more severe clinical feature than those with negative ASST [7, 8].

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.* [9] 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, 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. Thus, TFT alone is not enough to rule out thyroid disease and the thyroid antibody test should be carried out in all chronic Urticaria 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 high level of IgE may play a role in the pathogenesis of Chronic Autoimmune Urticaria (CAU) due to over expression of IgE receptor FaRla which will bind to IgE autoantibodies. Another proof for the role of the high level IgE in CAU is the study conducted by Azim, *et al.* showed improvement of 7 of 12 patients with CAU by anti-IgE, omalizumab which selectively binds to IgE. Kaplan. *et al.* postulated that omalizumab by decreasing circulating IgE level, will secondarily decrease IgE receptor density on basophils and cutaneous mast cells, preventing activation by autoantibodies [10].

Conclusion

In our setting, ASST is the only available test for the diagnosis of autoimmune Urticaria. It is simple, inexpensive, semi invasive and easy to perform, which can be done and recorded by the dermatologist himself to determine whether the patient's chronic Urticaria is autoimmune in origin. As conventional approaches of management may be unsuccessful, ASST is especially important from the therapeutic point of view as it can help to initiate immunosuppressive therapy in such patients.

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