



Chronic Idiopathic Urticaria-Correlation of Clinical Features with Autologous Serum Skin Test

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Abstract

Background: Chronic idiopathic urticaria, is characterized by Occurrence of recurrent episodes of hives for more than 6 weeks. Subgroup of chronic idiopathic urticaria is autoimmune.

Aim: To compare the clinical features in CIU patients with a positive autologous serum skin test (ASST) and negative ASST.

Methods: Hundred clinically diagnosed patients of CIU attending the department of dermatology OPD at tertiary care teaching hospital, were enrolled based on the inclusion and exclusion criteria.

Results: Proportion of patients with C/c idiopathic urticaria who showed positive reaction to ASST was 36%. Mean age of presentation was 32 years. In our clinical study of 100 patients, 53 were males and 47 were females. Angioedema occurred in 20 out of 100 patients.

Conclusions: In the present study ASST was positive in 36 % of patients with CIU. ASST positive patients had significant higher itch scores compared to ASST negative patients. Wheals involved significantly more sites and lasted for longer duration in ASST positive subgroup. ASST is a fairly good indicator of autoimmune etiology for chronic urticaria. It is a simple, inexpensive, semi invasive and easy to perform test.

Keywords: Chronic idiopathic urticaria; Autoimmune; CIU patients

Introduction

Chronic idiopathic urticaria, is characterized by occurrence of recurrent episodes of short lived urticaria (hives) on most of days of the week for a period exceeding 6 weeks. Associated angioedema occurs in around 40% of patients. CIU excludes the category of Urticaria induced by physical stimuli such as heat, cold, vibration, pressure, sunlight etc, the majority of the patients with chronic urticaria have an unknown or idiopathic etiology. This is referred to as chronic idiopathic urticaria or more recently, as chronic spontaneous urticaria (CSU) [1,2]. Subgroup of chronic idiopathic urticaria is autoimmune urticaria. The autoimmune subgroup of CIU is caused by IgG antibody to the alpha subunit of the Ig E receptor (35% to 40%), or IgG antibody to IgE (5% to 10%). that causes to mast cell and basophil activation, thereby leading to the release of histamine and other pro inflammatory mediators [3]. It is often not possible to

distinguish CAU from those without autoantibodies either clinically or histologically [4]. The gold standard diagnostic test for detecting clinically relevant autoantibodies to FcεR1α is the functional in-vitro donor basophil histamine assay [4]. However, this bioassay is difficult to standardize as it requires fresh basophils from healthy donors and is time consuming [3-8]. Autologous serum skin test (ASST) is a simple in-vivo clinical test for the detection of basophil histamine releasing activity and to diagnose chronic autoimmune urticaria (CAU) among chronic spontaneous urticaria (CSU) patients [5,9,10].

Aims of the study

- To find the proportion of patients with chronic idiopathic urticaria having autoantibodies in their sera using Autologous Serum Skin Test [ASST].
- To compare the clinical features of patients with and without autoantibodies

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Materials and Methods

Hundred patients of chronic idiopathic urticaria attending to the department of skin and STD, Medical College hospital, Calicut was enrolled for the study. The period of study was 12 months from August 2008 to August 2009.

In all the patients' physical urticaria, food allergy, drug allergy and urticarial vasculitis will be ruled out with the help of detailed clinical history and relevant laboratory investigations. In all patients, short acting antihistamines will be withdrawn, 2 days prior to testing and doxepin 2 weeks prior to the skin test to avoid false negative results.

Study design

Prospective observational study

Inclusion criteria

- Patients with recurrent urticarial wheals of > 6 weeks duration
- Age 12 and above

Exclusion criteria

- All patients on antihistamines for a period of 48hrs prior to test.
- Patients with history of physical urticaria
- Patients with urticarial vasculitis
- Patients with known Type 1 hypersensitivity reaction
- Pregnant females

Materials used for autologous serum skin test

- Centrifuged sera of patient
- Histamine 10ug/ml [prepared in hospital pharmacy]
- Sterile normal saline (0.9%)

Methodology of ASST

A 5ml of venous blood was collected in a sterile test tube without clotting accelerator and allowed to clot at room temperature for 30 minutes. Serum was sent to clinical laboratory for centrifugation at 2000rpm for 15mts. Samples of 0.05ml of autologous serum, and 0.9% sterile normal saline were separately injected intra dermally into volar aspect of right forearm with a gap of 5cm between injection sites. 0.05ml of histamine [10ug/ml] was injected into volar aspect of left forearm as positive control. Wheal and flare response was measured at 30 minutes. Positive ASST was defined as serum induced wheal which is both red and has a diameter of > 1.5mm than saline induced response at 30mts.

Statistical analysis

Descriptive statistics is used to summarize data for comparison between ASST positive and ASST negative group. Chi square test is used for categorical variables and non-parametric test is used for other variables.

Observations

Hundred patients satisfying the study criteria were enrolled in the study. Out of 100 patients, 36 patients (36%) showed a positive reaction to autologous serum skin test in the form of wheal and flare response, which was 1.5mm more than saline induced wheal, read at 30 minutes.

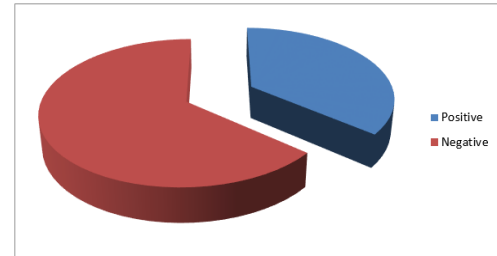


Figure 1: Observations of the 100 patients.

Clinical Characteristics

Age distribution

Mean age of patients was 32 with a range of 16 years to 62 years. There was no significant difference in age distribution between ASST positive and negative patients (t test, p-0.494). Mean age at ASST Positive patients 31.14 (SD 11.62, SE 1.94). Mean age of ASST negative patients 32.75 (SD 20.58, SE of mean 1.38).

Table 1: Age distribution.

Age distribution (Years)	ASST	
	Positive	Negative
12-20	8	9
21-30	11	23
31-40	12	21
41-50	2	6
>50	3	5

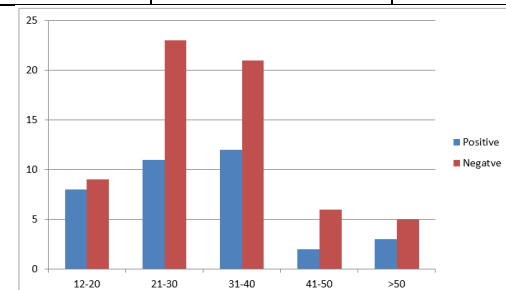


Figure 2: Age distribution of Patients.

Sex distribution

Of the total 100 patients, 53 were males and 47 females. 22 out of 36 (61.1%) ASST Positive and 25 out of 64 (39.1%) were females. Statistically significant proportion of females shows positive response to ASST (P value 0.034, chi-square test).

Table 2: Sex distribution.

Sex	ASST	
	Positive	Negative
Male	14 (38.9%)	39 (60.9%)
Female	22 (61.1%)	25 (39.1%)

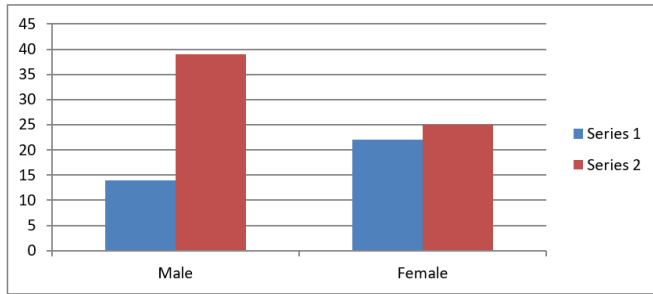


Figure 3: Sex distribution of Patients.

Duration of disease

Mean duration was 24.94 and 29.50 in ASST positive and ASST negative groups respectively. There was no significant difference in duration of disease between the two groups (t test).

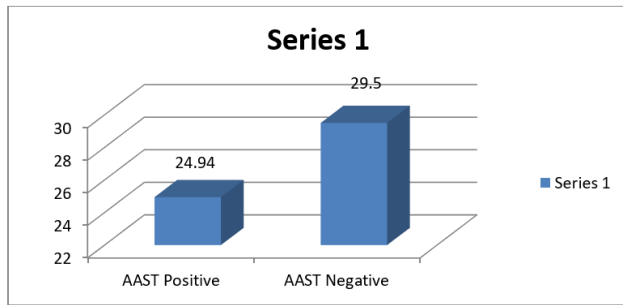


Figure 4: Duration of disease in ASST groups.

Angioedema

A 20 out of 100 patients gave history of angioedema. There was no significant difference in the incidence between ASST positive and ASST negative patients (Chi-square test). 9 out of 34 patients (25%) with positive ASST had history of angioedema whereas 11 out of 64 ASST (17.2%) negative patients also had history of angioedema. Five parameters of disease activity was recorded on 0-3 scale. Each parameters of both groups of patient (ASST positive Vs. ASST negative) were compared.

Table 3: Parameters of disease.

Parameter	Scores			
	0	1	2	3
No. of wheals	None	<10	11-50	>50
Duration of persistence	None	<1	1-12 hr	>12hrs
Intensity of itching	None	Mild	Moderate	Severe
Frequency of appearance	None	<1/week	1-3/week	Daily
Extend of lesion	None	<10%	11-50%	>50%

No. of wheals

Among ASST positive patients only 1 patient (2.8%) had score of 0 whereas 14 patients of ASST negative group had score of 1. Among ASST positive patients 22 patients (61.1%) and 13 (36.1%) had score of 2 and 3 respectively (Table 4). So statistically significant number of ASST positive patients had more number of lesion (P-0.029, chi-square test).

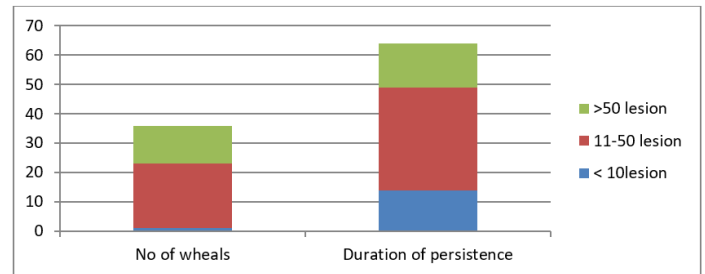


Figure 5: No of wheals and Duration of persistence in ASST groups.

Duration of persistence of lesions

Among ASST Positive patients out of 36 patients 16 (44.4%) and 20 (55.6%) had score of 2 and 3 respectively. There is statistically significant difference in the duration of persistence of disease between ASST positive and negative patients (Chi-square test P<0.05).

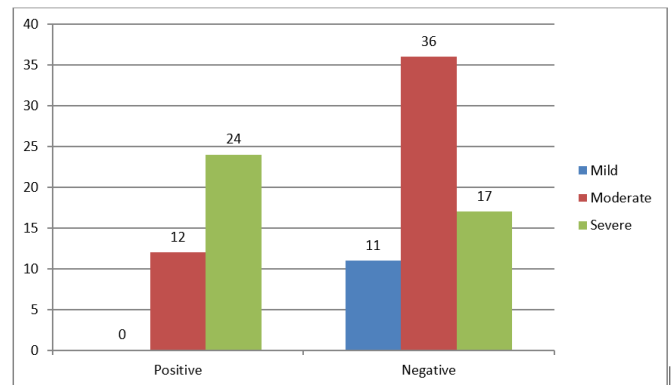


Figure 6: Significant difference in the duration of persistence of disease between ASST positive and negative patients.

Table 4: No. of lesions.

	No. of lesions		
	< 10 lesion	11-50 lesion	>50 lesion
No of wheals	1 (2.8%)	22 (61.1%)	13 (36.1%)
Duration of persistence	14 (21.9%)	35 (54.7%)	15 (23.4%)

Table 5: Duration of persistence of lesions.

	<1 hour	1-12 hours	>12 hours
Positive	-	16 (44.4%)	20 (55.6%)
Negative	16	36	12

Intensity of itching

Among ASST positive subgroup out of 34 patients, 12 and 24 patients had score of 2 and 3 respectively. None had a score of 1 whereas among ASST negative subgroup 11 patients had score of 1. Statistically significant proportion of ASST positive patients had severe itching (chi square test $P < 0.05$).

Table 6: Intensity of itching.

	itching		
	Mild	Moderate	Severe
Positive	-	12 (33.3%)	24 (66.7%)
Negative	11 (17.2%)	36 (56.3%)	17 (26.6%)

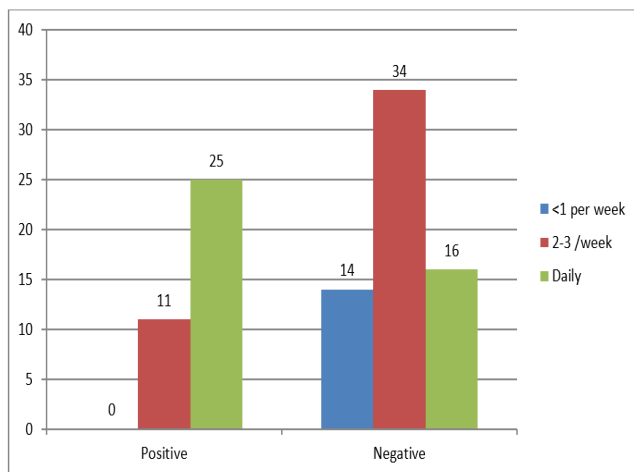


Figure 7: Frequency of appearance.

Frequency of appearance

Among ASST positive subgroup, 11 patients had 2-3 episodes per week and 25 patients had occurrence of lesions daily. There is statistically significant difference in frequency of appearance of lesion among ASST positive and negative patients.

Table 7: Frequency.

	Frequency		
	<1 per week	2-3 / week	Daily
Positive	-	11 (30.6%)	25 (69.4%)
Negative	14 (21.9%)	34 (53.1%)	16 (25%)

Extend of body involvement

Among ASST positive subgroup, 17 out of 36 patients had score of 2 and the rest of 19 patients had score of 3. There is statistically significant difference in the percentage of body surface and involvement between ASST positive and negative patients (Chi square test $P < 0.05$).

Table 8: Extend of body.

	Extend		
	1-10%	11-50%	>50%
Positive	-	17 (47.2%)	19 (52.8%)
Negative	15 (23.4%)	36 (56.3%)	13 (20.3%)

ANA testing

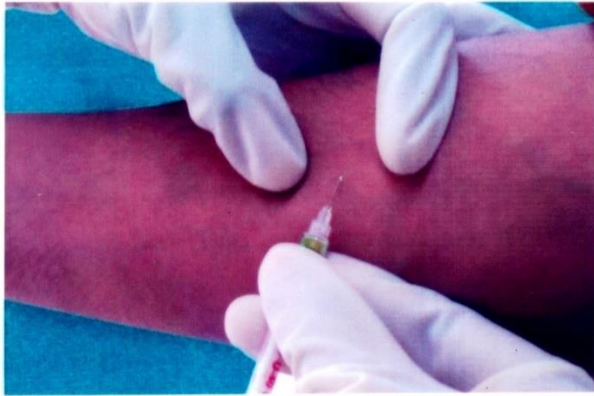
ANA was done for 10 patients and was positive for one patient. No significant correlation was noted with ASST.



Clotted blood sample



Sample for centrifugation



Intradermal injection of 0.05ml of serum on flexural aspect of forearm

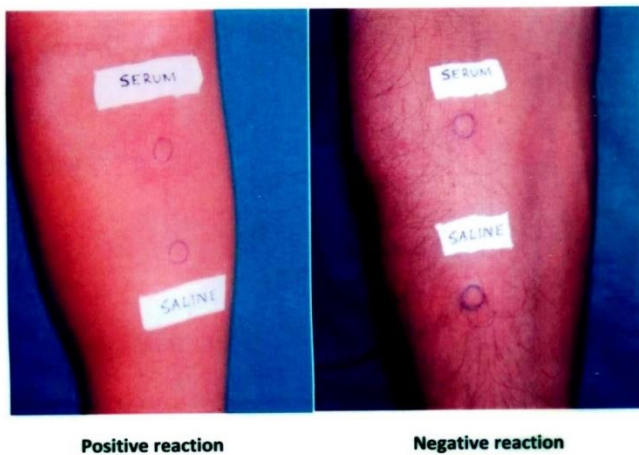


Figure 8: Thyroid function test.

Thyroid function test

Abnormal TFT was obtained in two out of ten patients tested. There was no significant correlation with ASST result.

Discussion

The present study has evaluated patients with chronic idiopathic urticaria by autologous serum skin testing and compared the clinical features of patients with positive and negative ASST results. Proportion of patients with C/c idiopathic urticaria who showed positive reaction to ASST was 36% which is comparable with earlier results.

Sabore et al reported that one third of their patients with CIU had circulating functional antibody against high affinity IgE receptor FCER1 and or IGE. Asero et al reported that 205 out of 306 (67%) Italian patients with CIU showed positive ASST. Bajaj et al reported 49.5%) had positive reaction to autologous serum. Mamata et al reported 34% had positive reaction to autologous serum.

It is now established that circulating autoantibodies against high affinity IgE receptor (FceRI) or against IgE can be found in approximately one third of patients with CIU". These antibodies are functional. It has been demonstrated both in vivo and in vitro by induction of wheal and flare response to intradermal injection of serum (ASST) and basophil histamine release assay respectively. In addition, removal of autoantibodies by plasmapheresis has been shown to produce clinical improvement in patients with CIU98. Clinical features of patients with CIU were defined in several studies before the identification of autoantibodies [6,7]. Now it is known that there are at least two subset of patients with CIU - those with and without antibodies. We have evaluated clinical features and disease severity to establish whether disease mechanism influence clinical presentation.

Sex distribution

In our clinical study of 100 patients, 53 were males and 47 were females. Among ASST positive patients, 22 were females (61%) and 14 were males (38.9%). Thus there is a statistically significant higher proportion of females among ASST positive group.

	Sabore et al	Mamata et al	Present study
/Male / Female	88/19	44/56	53/47

Age

Mean age of presentation was 32 years and age ranged from 16 years to 62 years. This is comparable to previous studies. Mean age of presentation was 31 and 33 in ASST positive and negative group respectively.

	Sabore et al	Mamata et al	Present study
Mean age of presentation	45	34	32

Duration of disease

Mean duration of disease was 25 months and 30 months for ASST positive and negative patients respectively. It was not statistically significant. So our study in comparison to previous studies didn't demonstrate any statistically significant difference between ASST positive and negative patients in mean age of presentation and duration of disease.

	Sabore et al	Mamata et al	Present study
ASST +ve	10M	12M	25M
ASST -ve	22.5M	15M	29.5 M

Angioedema

Angioedema occurred in 20 out of 100 patients. There was no significant difference between patients with or without antibodies, in the incidence, duration, frequency or distribution of angioedema.

Sabore et al	Mamata et al	Present study
93/107	15/100	20/100

Severity of urticaria

Majority of parameters examined to define severity of urticaria showed significant difference between ASST positive and negative groups. Like number of wheals, area of body involvement, and frequency of attacks, intensity of itching and duration of persistence of wheals. Each of these five parameters were given a score ranging from 0 to 3 according to severity. ASST positive patients had higher scores compared to ASST negative patients for each of above five parameters i.e. ASST positive patients had statistically significant higher number of wheals and more frequent attacks.

ASST positive patients had significant higher itch scores compared to ASST negative patients. Wheals involved significantly more sites and lasted for longer duration in ASST positive subgroups. Sabore et al reported in 1999 that patients with autoantibodies had more severe urticaria than patients without autoantibodies according to several parameters. They had higher urticaria scores, urticaria involved more sites; it was itchier. They also had frequent long lasting episode this finding is in concordance with our study. However, most of other reports have revealed only subtle difference in symptomatology of ASST (+) and ASST (-) patients.

Patients with autoantibodies have significantly more systemic symptoms than those without autoantibodies. In particular gastrointestinal symptoms and flushing occur more frequently in patients with autoantibodies. But in our clinical study we did not find any such association.

Autoimmune diseases like thyroid diseases, vitiligo, insulin dependent diabetes mellitus, pernicious anemia and rheumatoid arthritis were reported more commonly in patients with autoimmune urticaria. In our study of 10 patients tested, positive ANA was found in one patient who also had positive ASST. We did not find an increased incidence of other autoimmune diseases in our clinical study.

In our study out of 10 patients tested abnormal TFT values were detected in two patients. Association of chronic urticaria with thyroid autoimmunity has been studied by Leznoff et al. It has been postulated that thyroid autoimmunity may play a role in the pathogenesis of chronic urticaria and angioedema. However in contrast with previous studies, we did not detect a difference in

the incidence of thyroid disease. This is likely because insufficient numbers of patients were included for the study a disease of low incidence (thyroid autoimmunity occurs in less than 6% of general population) or because thyroid function tests and thyroid autoantibodies were not routinely measured, and subclinical thyroid disease or a asymptomatic elevations in thyroid antibody titers would have been missed. Thus TFT alone is not enough to rule out thyroid disease and thyroid antibody test should be carried out in all CIU patients.

In our setting ASST is the only available tests for the diagnosis of autoimmune urticaria. It is a simple, inexpensive, semi invasive and easy to perform test which can be done and recorded by the dermatologist himself to determine whether the patients CIU is autoimmune in origin. ASST is especially important from the therapeutic point of view as it can help the dermatologist to initiate immunosuppressive therapy to such patients.

Conclusions

1. Autoantibodies, detected by ASST, were seen in sera of 36% patients with CIU, comparable to available reports in literature.
2. Presence of these autoantibodies was
 - a. Significantly associated with more frequent and longer lasting urticarial attacks
 - b. Significantly associated with more number of wheals and is associated with higher itch scores
 - c. Wheals significantly involved higher body surface area d. Unrelated to age, sex, duration of disease and angioedema
3. There was no correlation between ASST positivity and other autoimmune disorders tested i.e., Thyroid dysfunction and ANA. However this may be due to inadequate number of patients tested.
4. Thus ASST identifies a subgroup of patients with CIU with more severe disease, who are likely to be more symptomatic and would require more aggressive treatment.

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SUNTEXT REVIEWS

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