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Original Research Article

Chronic idiopathic urticaria and autoimmunity: frequency and association in patients with positive versus negative autologous serum skin test

Rashmi Jindal*, Samarjit Roy, Prateek Nagrani

Department of Dermatology, Venereology and Leprosy, Himalayan Institute of Medical Sciences, Swami Rama Himalayan University, Dehradun, Uttarakhand, India

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***Correspondence:**
Dr. Rashmi Jindal,
E-mail: rashmijindal98@gmail.com

ABSTRACT

Background: Chronic idiopathic urticaria is a subset of urticaria where no known trigger is identifiable. Almost half of these patients have an autoimmune basis of their disease. Autologous serum skin test (ASST) is an easy to perform test to identify this subgroup. However, frequency and association of positive ASST with other markers of autoimmunity remains to be studied. The present study was aimed to find out the same.
Methods: Chronic idiopathic urticaria patients were divided into two groups on the basis of ASST. These were further compared for their clinical characteristics including age, gender, duration of disease and urticaria activity score. Also investigation profile including serum IgE levels, anti TPO antibodies, antiTSH and antinuclear antibodies were compared.
Results: There were no statistical differences in the age, gender, duration of disease and urticaria activity score in the ASST positive and negative patients. Serum IgE levels though lower in ASST positive group were not statistically different. Frequencies of AntiTPo antibodies, antiTSH and antinuclear antibodies were also comparable in the two groups.
Conclusions: ASST positive and negative groups can't be distinguished clinically. Also autoimmunity was found to be associated with both ASST positive and negative groups.

Keywords: Autologous serum skin test, Autoimmunity, Urticaria

INTRODUCTION

Chronic urticaria (CU) is characterized by development of wheals recurring daily or almost daily for more than six weeks. It affects 0.1-1.0% of the general population.[1] Chronic idiopathic urticaria (CIU) is a subset of urticaria where no known trigger is identifiable and it constitutes the largest subgroup of total CU patients. Further around 50% patients of CIU have a functional complement activating autoantibody directed against high affinity receptors of IgE or IgE itself.[2,3] These patients are said to have chronic autoimmune urticaria (CAU). Autologous serum skin test (ASST) or basophil release assay are done to detect the presence of such autoantibodies. Because of the time consuming nature and difficulties in standardization of basophil histamine release assay, it is not widely used. On the other hand ASST is an easy outpatient test, which is gaining popularity these days. Sensitivity of ASST is 70% and specificity is around 80%.[4] In general it is expected that the patients with positive ASST will have a severe course of disease and they will require higher doses of antihistamines along

with immunomodulatory drugs for disease control. Thus ASST holds a prognostic importance. However, whether positivity of ASST is also reflected in other immunological markers such as serum IgE levels, presence of antithyroid autoantibodies and antinuclear antibodies (ANA) is yet to be ascertained. The present study was aimed at finding out the frequency and association of these immunological markers in ASST positive versus ASST negative patients of CIU. This might help in deciding the approach to a patient of CIU. If ASST positive patients are found to have significant association with these immunological markers, then there will be no need to subject ASST negative patients to such a vast array of investigations. This will further cut down the economic burden of the disease.

METHODS

Fifty consecutive patients with clinical diagnosis of CIU were enrolled for the study. Children aged <12 years and pregnant/ lactating women were excluded. Patients of acute urticaria, urticarial vasculitis or those having systemic diseases known to cause urticaria were excluded. Written informed consent was taken from all patients and ethical clearance for the study was taken from the institutional ethical committee.

A detailed history of disease including duration of disease, associated angioedema and history of atopy and frequency of attacks was noted on a predesigned proforma. A complete general physical examination and dermatological examination was performed in all patients. Severity of urticaria was assessed using the urticaria activity score (Table 1).

Laboratory tests included complete blood counts, ESR, C-reactive protein levels, TSH, serum IgE levels, antiTPO and antiTSH antibodies and antinuclear antibodies (ANA). An ASST was performed in all patients according to the standard technique after stopping antihistamines three days prior and steroids and other immunomodulators three weeks prior to the test.[5] 0.05ml of autologous serum and 0.05ml of normal saline were injected intradermally into the volar aspect of forearm. A positive ASST was labelled when the average diameter of red serum induced wheal was ≥1.5mm of the normal saline induced wheal measured after 30 minutes. On the basis of the result of ASST, two groups were then compared for their clinical features and laboratory parameters.

Statistical analysis

Data was recorded and processed using SPSS version 12.0. Quantitative variables were expressed as mean (SD) and were compared using paired t-test. Qualitative variables were expressed as frequencies and were compared using chi-square test when appropriate. A p-value of <0.05 was considered significant.

RESULTS

The ASST was positive in 20 patients (40%) and negative in 30 patients (60%). The mean age of patients in ASST positive group was 31.85±12.32 years and ASST negative group was 34.40±11.38 years.

Table 1: Urticaria activity score.

Parameter	0	1	2	3
Number of wheals	None	≤10	11-50	>50
Size of wheals	None	<1cm	1-3cm	>3cm
Intensity of pruritus	None	Mild	Moderate	Severe
Duration of persistence	None	<1h	1-12h	>12h
Frequency of appearance	None	<once or once a week	2-3 times a week	Daily/ almost daily
Frequency of antihistamine use	None	<once or once a week	2-3 times a week	Daily/ almost daily

Total score= Addition of scores of each parameter.

Table 2: Characteristics of chronic idiopathic urticaria patients.

	Positive ASST (n=20)	Negative ASST (n=30)	P-value
Age (years)			
Range	14-56	14-57	
Mean (SD)	31.85(12.32)	34.40(11.38)	0.456
Sex No. (%)			
Females	11(55)	21(70)	
Males	09(45)	09(30)	0.37
Duration of disease (months)			
Range	3-180	3-300	
Mean(SD)	43.25(48.55)	34.47(53.57)	0.559
Angioedema, No.(%)	9(45%)	13(43.3%)	1.00
Atopy, No.(%)	1(5%)	1(3.3%)	1.00
Urticaria activity score			
Range	10-18	09-18	
Mean(SD)	14.70(2.29)	13.50(2.12)	0.065

The mean duration of disease in ASST positive group was 43.25±48.55 months while that in ASST negative group was 34.47±53.57 months. The mean duration of disease though was longer in ASST positive group however this difference was not statistically significant.

On comparing the ASST positive versus ASST negative group no significant difference was found in gender, history of atopy or presence of angioedema. The urticaria

activity score was also found to be comparable in the two groups (Table 2). Serum IgE levels were lower in ASST positive patients although this could not attain statistical significance (p=0.06). Further no statistical difference was found in the frequencies of antiTSH, antiTPO and antinuclear antibodies between the two groups. The values of ESR, CRP and TSH were also comparable (Table 3).

Table 3: Immunological and laboratory test results.

	Positive ASST (n=20)	Negative ASST (n=30)	P-value
Serum IgE (IU/ml)			
Range	05-402.74	5-800	
Mean (SD)	77.81 (82.92)	162.56 (185.44)	0.061
AntiTPO antibody			
No. (%)	3(15%)	5(16.7%)	1.00
AntiTSH antibody			
No. (%)	2(10%)	3(10%)	1.00
Antinuclear antibody			
No. (%)	1(5%)	3(10%)	0.641
ESR (mm in 1st hour)			
Range	2-89	1-52	
Mean (SD)	23.85 (23.48)	17.23 (12.38)	0.20
C-reactive protein (mg/l)			
Range	0.1-15.17	0.1-23	
Mean (SD)	2.98(3.99)	3.11(5.02)	0.922
TSH (µIU/ml)			
Range mean (SD)	2.79 (1.81)	8.93 (24.78)	0.277

ESR= erythrocyte sedimentation rate; TSH= thyroid stimulating hormone;TPO= thyroid peroxidase

DISCUSSION

Autologous serum skin test is simple, cost effective and easy to perform. Results of ASST are available with in 30 minutes and thus it can be used as an effective tool to identify patients with an underlying autoimmune basis of the disease. This further can help in justifying the use of high doses of antihistamines or other immunomodulators including steroids. The results of ASST showed that 40% of our patients had CAU. Other studies have reported the prevalence of positive ASST to vary from 34% to 67%.[6-8] There was no significant difference between the two groups for age, gender, and presence of angioedema or history of atopy. These findings correlate well with those previously reported by Kulthanan et al and George et al.[9,10] Duration of disease was found to be significantly longer in patients with positive ASST by Sabroe et al and Azim et al.[5,11] We also found the duration of disease to be longer in ASST positive group however; this could not reach a statistically significant level. UAS were comparable in the two groups. This is consistent with findings of Bajaj et al and Azim et al.[11,12] However, Caproni et al reported more severe clinical features in patients with positive ASST.[6] The above findings thus suggest that the patients of positive and negative ASST cannot be distinguished clinically.

The serum IgE levels were lower in patients with positive ASST though this difference was not statistically significant. Huilan et al also reported lower levels of serum IgE in ASST positive patients.[13] This was explained on the basis of formation of IgE-antiIgE immune complexes due to which amount of free IgE were reduced in patients having anti IgE antibodies. Other researchers have reported contrasting results with significantly higher serum IgE values in ASST positive patients.[14,15]

Thyroid disease was previously reported to be associated with chronic urticaria. Leznoff et al reported significantly higher levels of antithyroid microsomal antibodies in patients with chronic urticaria when compared to control population.[16] In present study, antiTPO antibodies were raised in 15% and 16.7% patients of ASST positive and ASST negative groups respectively. AntiTSH antibodies were detected in high titers in 10% patients in both groups. Thus there was no statistically significant difference in detection of antithyroid antibodies in the two groups. Our findings are comparable to that reported by Yadav et al.[17] However, Bakos et al and O'Donell et al have reported significant association between detection of antiTPO antibodies and ASST positivity.[18,19]

Similar to antithyroid antibodies, antinuclear antibodies were also not found to have any significant association with ASST positivity. 5% patients of ASST positive group and 10% patients of ASST negative group had ANA positivity. Thus autoimmunity was found to be associated with both ASST positive and ASST negative groups. Yadav et al have proposed possible explanations for this observations.[17] When patients with thyroid autoimmunity go into remission they will be ASST negative but can still continue to have detectable levels of antithyroid antibodies. Further they explained that probably in ASST negative patients the histamine releasing factor, which is as yet uncharacterized, is an autoantibody.

To summarize, there are no distinctive clinical or laboratory parameters specifically associated with ASST positivity. ASST positive and negative patients could actually represent a continuum of the same disease. There is need to follow patients of CIU with repeat ASST, so as to ascertain whether the findings change over time. Further research should be carried out to find the as yet unidentified histamine releasing factor.

The major limitations of our study are small sample size. Further categorization of the study groups was done only on the basis of ASST which has a sensitivity of 70% when compared to basophil histamine release assay.

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