Chronic Idiopathic Urticaria and Thyroid Autoimmunity: Perplexing Association

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Abstract

Background: Autologous serum skin test (ASST) is the most commonly used laboratory test to differentiate chronic autoimmune urticaria patients from chronic idiopathic urticaria patients without autoantibodies. Thyroid autoimmunity is the original paradigm for autoimmune disease in general and many previous studies show increased prevalence of thyroid autoantibodies and deranged thyroid hormone profile in chronic idiopathic urticaria patients. **Aim:** To find the association between thyroid autoimmunity and chronic autoimmune urticaria, if any. **Materials and Methods:** The chronic idiopathic urticaria patients were divided into two subgroups based on autologous serum skin test. Thyroid autoantibodies were estimated in 40 patients each of ASST positive and ASST negative groups. Further, thyroid hormone profile was done in cases with significant titers of thyroid autoantibodies. Forty patients, who had never suffered from urticaria, represented the control group. **Results:** The prevalence of thyroid autoantibodies did not differ significantly among the ASST positive (20%) and ASST negative patients (15%). The control group had low prevalence of these autoantibodies (5%). **Conclusion:** The almost equal prevalence of thyroid autoantibodies in two subgroups of chronic idiopathic urticaria patients suggests possibly the same etiopathogenesis of the two subgroups. The two subgroups probably form a continuum, or even may be the same entity.

Key Words: *Autoimmune urticaria, chronic idiopathic urticaria, thyroid autoimmunity*

What was known?
1. Around one third CIU patients have chronic autoimmune urticaria.
2. Thyroid autoimmunity is associated with Chronic urticaria.

Introduction

Chronic urticaria (CU) is defined as urticaria persisting daily or almost daily for more than six weeks. The pathophysiology of CU is not completely understood, although most agree that the central event is activation of cutaneous mast cells. CU includes physical urticaria, chronic "idiopathic" urticaria (CIU) and urticarial vasculitis. CIU patients do not have a clinically identifiable trigger and they constitute the largest subgroup of total CU patients. Within this group, 25-55% of patients have functional complement-activating autoantibodies directed against the high-affinity receptor for IgE (FcεRI) or at IgE itself, and are said to have chronic autoimmune urticaria (CAU).[1-6] These autoantibodies can be detected by *in-vivo* test like Autologous serum skin test (ASST) and *in-vitro* tests including donor basophil histamine release assay, detection of donor basophil CD203c expression using flow cytometry, and ELISA techniques.

Thyroid autoimmunity appears to occur more frequently in patients with autoimmune skin diseases such as alopecia areata and vitiligo and in other nondermatologic immunologic diseases such as type I diabetes mellitus and Addison's disease. Association of autoimmune thyroid disease with CIU is unresolved mystery. Approximately 5-34% of patients with CIU have antithyroid antibodies and another 5-10% have clinically or biochemically apparent thyroid disease.[7-9] These autoantibodies are directed against either thyroid peroxidase (TPO) or thyroglobulin or TSH receptor. There is evidence for relationship between degree of inflammation in thyroid and presence of urticaria.[10]

However, it is not known whether the presence of thyroid autoimmunity in patients with CIU is in corollary with the association of thyroid autoimmunity with other autoimmune diseases and in that case the antithyroid antibodies should preferentially be found in CAU patients. There are only 3 previous studies which have investigated the association of thyroid autoimmunity specifically with CAU.[11-13]

We did this study to get further insight into this association as that would help in delineating the battery of investigations in CIU patients. In the clinical setting, ASST is the most commonly performed *in-vivo* test to distinguish CIU patients having auto-antibodies from those without autoantibodies because of its low cost and ease of performance. If thyroid autoimmunity is associated with only CAU then we should subject only ASST positive patients to further testing for thyroid autoantibodies and thyroid function testing in case the patient is clinically euthyroid.

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Materials and Methods

Patients and study design

The study enrolled patients with clinical diagnosis of CIU in the age group of 15-50 years, attending the urticaria clinic of the Department of Dermatology, at the Post Graduate Institute of Medical Education and Research, Chandigarh. Informed written consent was taken from all the subjects enrolled in the study. All the patients were assessed clinically and detailed history of their illness and associated systemic complaints was taken.

These patients were then subjected to ASST and 40 patients each with ASST negative and positive results were included in the study. Patients were advised to stop antihistamines three days prior and steroids three weeks prior to ASST. Patients giving history of anaphylaxis, concomitant autoimmune disease, having marked component of associated physical urticaria, or having other concomitant dermatoses involving the skin of forearm were excluded from the study. ASST was performed according to the standard technique described previously.[14] Samples (50μL) of autologous serum, 0.9% sterile saline and histamine solution (10 μg/ml) were separately injected intradermal into the volar aspect of the forearm. Wheal diameter was measured after 30 min. ASST was considered as positive if the average diameter of the red serum-induced wheal was ≥ 1.5 mm of the normal saline-induced wheal [Figures 1 and 2].

Forty age and sex matched healthy subjects who had given consent for the study were enrolled in the control group (hospital staff, patients presenting with unrelated complaints, relatives and attendants of patients). These subjects also underwent ASST.

Thyroid autoantibodies

All the subjects of study were further evaluated for the presence of thyroid autoantibodies (anti TPO) using ELISA technique (EUROIMMUNE, Medizinische Labordiagnostika AG) and the test was performed using the manufacturer's instructions.

Thyroid hormone profile

Thyroid hormone profile including thyroid stimulating hormone, free T_3, free T_4 was done for all the subjects who tested positive for thyroid autoantibodies.

Statistical analysis

Statistical analysis was performed using SPSS for windows version 11.0. The results were analyzed using Chi-square test, Student *t*-test and Anova test and significance was defined as $P < 0.05$.

Results

The mean age of patients in ASST positive group (32.5 years) and ASST negative group (33 years) were similar to the control group (30.5 years). There were almost equal number of males and females in ASST positive (M:F = 1:1.22) and ASST negative (M:F = 1:1.35) groups. The presenting complaints of both the subgroups of patients were wheals associated with pruritus. Mean duration of illness in the ASST positive and ASST negative subgroups were 3.25 and 3.5 years respectively. Angioedema was equally common in the two subgroups. Mean urticaria activity score was higher in ASST positive group (6.8 ± 1.2) than the ASST negative group (6.2 ± 1.4) but the difference was not significant. Family history of urticaria was present only in ASST positive patients (4 out of 40 patients). In the control group ASST was positive in 4 (10%) cases. One of them had personal history of atopy.

Of the total 80 CIU patients included in the study, 14 (17.5%) tested positive for anti TPO autoantibodies. Table 1 shows the epidemiological characteristics, results of anti TPO autoantibodies titers, ASST and thyroid hormone profile in subjects who had significant titers of anti TPO autoantibodies. Females outnumbered males with male to female ratio of 1:1.4.

Eight (20%) of the 40 ASST positive patients, 6 (15%) of the 40 ASST negative patients and 2 (5%) of 40

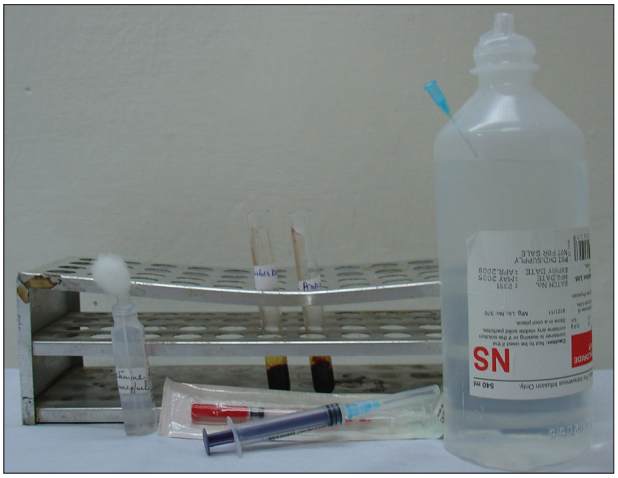

Figure 1: Material required for doing ASST

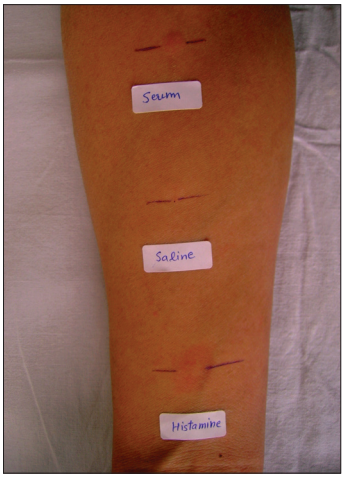

Figure 2: Positive ASST at 30 min

control group had significant titers of anti TPO auto antibodies [Table 2]. The difference between ASST positive and ASST negative groups was not significant; however, the difference between ASST positive group and the control group was statistically significant (*P* value-0.043).

Thyroid hormone profile was done in those cases that had significant titers of anti TPO autoantibodies. Among the ASST positive group, one patient was lost to follow up and four out of seven patients had deranged thyroid hormone profile [Table 3]. Among the ASST negative group, thyroid hormone profile results were available for five patients and only one had deranged thyroid function test (TFT). Both the control cases having raised anti TPO autoantibody level had normal TFT results. Though larger number of patients in ASST positive group had deranged TFT compared to ASST negative group, the significance could not be established due to small number of subjects.

Table 1: Epidemiological characteristics, anti TPO autoantibodies titers, ASST and thyroid function test results in subjects with raised titers of anti TPO autoantibodies

Age	Sex	TPO IU/ml	ASST	T3	T4	TSH
16	F	214	+	1.08	40.00	5.40
43	F	1518	+	1.16	45.90	9.41
44	M	112	+	0.47	69.40	9.43
48	F	460	+	1.52	77.80	1.75
38	F	178	+	0.81	49.00	4.54
19	F	279	+	0.95	65.10	0.84
40	M	347	+	-	-	-
26	F	1094	+	1.10	130.30	0.81
28	M	93	-	1.13	124.10	3.97
39	F	382	-	-	-	-
50	F	802	-	1.46	98.60	3.64
36	F	114	-	1.07	131.00	4.05
32	M	2112	-	1.50	38.47	6.21
21	F	1471	-	1.56	116.00	2.82
Control						
48	M	191	-	2.00	80.60	2.25
30	F	178	-	1.50	84.00	1.26

(Normal values-T3-0.7-2 ng/ml, T4-55-135 ng/ml, TSH-0.17-4.05 µIU/ml), TPO: Thyroid peroxidase; ASST: Autologous serum skin test

Table 2: Distribution of cases with raised anti TPO levels among the three groups included in the study

	ASST+ve	ASST −ve	Control
Anti TPO + (%)	8 (20)	6 (15)	2 (5)
Anti TPO − (%)	32 (80)	34 (85)	38 (95)
Total	40	40	40

TPO: Thyroid peroxidase; ASST: Autologous serum skin test

Table 3: TFT results in cases with raised anti TPO titers

	ASST positive group	ASST negative group	Control
Deranged TFT	4	1	0
Normal TFT	3	4	2
Lost to follow up	1	1	0
Total	8	6	2

TFT: Thyroid function test; TPO: Thyroid peroxidase; ASST: Autologous serum skin test

Discussion

CIU is a disabling disease with usually a prolonged waxing and waning course. During last decade various studies have been done to gain insight into the pathogenesis of CIU. The concept of autoimmune urticaria has evolved over the past decade as evidence for histamine-releasing autoantibodies and their relationship to disease activity has accrued. This subset of urticaria patients have autoantibodies directed against either the high affinity IgE receptor (Fc∈RI), or less commonly against receptor bound IgE itself.[1-3] That the autoantibodies are functional, is supported by their ability to produce whealing after intradermal injection into the skin of human volunteers,[15] and ability to release histamine from healthy donor basophil and mast cells.[16,17] The percentage of patients with anti Fc∈RI autoantibodies varies from 25% to 55% of the total CIU patients.[1-6]

An increased frequency of CU was observed in patients with thyroid disease, and some patients with CU also showed evidence of an underlying autoimmune thyroid disease.[18,19] In 1983, a landmark study by Leznoff *et al*.[20] showed significantly increased levels of anti-thyroid microsomal antibodies (antiTMA) in CU patients compared to control population. This has been confirmed in the subsequent studies, with the prevalence varying from 12 to 33%.[21,22] Most of the studies done till date, show statistical association between CIU and thyroid autoimmunity, but only three previous studies have investigated the association specifically between CAU and thyroid autoimmunity.[11-13] In our study we segregated the CIU patients into two subgroups based on the results of ASST alone due to reasons mentioned before and also because of the non-availability of *in-vitro* assays to detect anti Fc∈RI or anti Ig E autoantibodies.

In our study, the mean age of patients in ASST positive and ASST negative group were comparable. Mean duration of illness and other clinical characteristics were also similar in the two groups. Many previous studies have suggested higher urticaria severity in ASST positive patients compared to ASST negative patients, but in our study the difference in severity score was not significant between the two groups.[4,5] Of the total 80 CIU patients 17.5% had raised anti TPO titers which is comparable to previous studies.[21-23] Autoimmune diseases have female preponderance and also, in our study females outnumbered males with male to female ratio of 1:1.4. In the ASST positive and ASST negative groups, 20% and 15% patients respectively had significant titers of thyroid autoantibodies and the difference between the two subgroups was not significant ($P < 0.05$). In the control group, 5% cases had raised anti TPO autoantibody titers.

In our study, thyroid autoimmunity was found to be associated with both ASST positive and ASST negative subgroups which is contradictory to results of studies by Bakos *et al*.[11] and O'Donnell *et al*.,[12] which demonstrated segregation of anti-thyroid antibodies with ASST positivity. Bakos *et al*.[11] included 48 CU patients and found that 42.3% of ASST positive group had raised anti TPO autoantibody titers, which was significantly greater than the 13.6% in ASST negative group. O'Donnell *et al*.,[12] studied 182 CIU patients; of them 90 had positive ASST. Eighteen (20%) of the ASST positive but only four (4.3%) of ASST negative group had raised antiTMA levels. The clustering of antiTMA positivity among the ASST positive patients was significant. O'Donnell *et al*., included larger number of females (69%) which were not equally distributed in the two subgroups, also there were no controls and they studied titers of antiTMA which is less specific and sensitive than anti TPO autoantibodies.[19,24]

Among ASST positive patients with raised anti TPO autoantibody levels, 50% had deranged TFT. While in ASST negative group only one of five patients with raised anti TPO antibody levels had deranged TFT. Significance of these findings can be established by studying larger number of patients. In the control group none of the cases with raised anti TPO level had deranged TFT.

Thyroid autoimmunity was found to be associated with both ASST positive and ASST negative groups. There are few plausible explanations for our findings. Disease course of chronic urticaria is unpredictable, characterized by remissions and relapses. How the autoantibody titers vary with the course of disease has not been studied till now. There are no definitive clinical or laboratory criteria to say that patient is in permanent remission. So some ASST positive patients with associated thyroid autoimmunity may become ASST negative later when the titers go down while the thyroid autoimmunity persists. Also, it may be possible that all CU patients have autoimmune basis and titers of autoantibodies vary in individuals from very low to high. The patients with low titers may give falsely negative ASST result. Hence, the thyroid autoimmunity might seem to be associated with both ASST positive and ASST negative subgroups of CIU patients.

It is possible that the yet uncharacterized histamine releasing factor in ASST negative patients is an autoantibody and so the association of the group with thyroid autoimmunity. This uncharacterized factor may be labile and is either degraded, or becomes inactive during the processing of serum.

Lastly, it could be that autoimmune thyroiditis has direct implication in the pathophysiology of urticaria which is independent of the presence of anti FcRI antibodies. Rumbyrt *et al*.,[25] proposed that an inflammatory response in the thyroid leads to a generalized inflammatory state and lowers the threshold of mast cells to other stimuli. And therefore, the association of thyroid autoimmunity may be present with both subgroups of CIU patients.

Bajaj *et al*.,[26] evaluated the efficacy of repeated autologous serum injections in patients with recalcitrant chronic urticaria. Higher number of patients in the ASST positive group (35.5%-completely asymptomatic, 24.2%-markedly improved) responded to therapy, but a significant number of patients in the ASST negative group (23%-completely asymptomatic, 23%-markedly improved) also showed response. The study supports our notion as ASST negative subgroup has also responded to autologous injection therapy.

There are two limitations of our study. First, we classified the CIU patients into two subgroups based on ASST alone. ASST has low sensitivity and specificity compared to *in-vitro* assays like donor basophil histamine release assay and mast cell histamine release assay. Another limitation of our study is that we tested for the presence of anti TPO alone for diagnosing thyroid autoimmunity. Testing for anti TSH in addition to anti TPO would have increased the detection of thyroid autoimmunity.

In summary, ASST positive and negative patients did not have distinctive diagnostic clinical feature and thyroid autoimmunity was found to be equally associated with the ASST positive and ASST negative subgroups. We have proposed few possible explanations for our observations. However, further research needs to be done to find if both ASST positive and ASST negative patients have autoimmune basis and whether these two groups actually form a continuum of same disease with difference in the titers of autoantibodies and have several other yet unidentified pathogenic histamine releasing factors.

What is new?
Thyroid autoimmunity was found to be associated with both ASST positive and ASST negative subgroups of CIU patients.

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