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Association of Autoimmunity in Autologous Serum Skin Test Positive and Negative Chronic Urticaria Cases.

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Abstract

Introduction: The Pathophysiology of Chronic Urticaria (CU) is not completely understood, although most agree that the central event is activation of cutaneous mast cells. The aim of this study is to evaluate the association of autoimmunity in autologous serum skin test (ASST) positive and negative chronic urticaria cases.

Materials and Methods: This is a hospital based, observational comparative analysis done on 264 patients (132 patients in each group) in the Department of Dermatology, Venereology and Leprosy**,** SMS hospital, Jaipur from March 2016 to October 2017. Two groups were made in our study, Group I: ASST Positive and Group II: ASST Negative. All baseline routine investigations and autoimmune profile were done in both groups.

Results: Our study showed a significant association between chronic urticaria ASST positive cases and thyroid auto-antibodies. Besides thyroid auto-antibodies, other auto-antibodies were not significantly associated.

Conclusion: Our study concludes that all patients with CU should be evaluated for ASST and the positive ASST cases should be further investigated for thyroid auto-antibodies; which may prove useful in management of treatment resistant cases.

Keywords: Chronic urticaria, ASST, Autoimmunity, Anti-TPO antibodies

Introduction

Urticaria is characterised by short lived swellings of skin and mucosa due to plasma leakage[1]. It affects 15-20% of the population once or more during a lifetime.[2] The Pathophysiology of Chronic Urticaria (CU) is not completely understood, although most agree that the central event is activation of cutaneous mast cells. This key Pathophysiological event is predominant at the immediate phase of inflammation, which progresses to a complex interplay of varied proinflammatory mediators, cytokines, chemokines, and adhesion molecules that regulate vasoactivity and specific kinetics of cellular infiltration, ultimately evolving into a lymphocyte and granulocytes mediated hypersensitivity reaction, evident as urticarial wheals[3]. Urticaria is classified into:-Acute <6weeks and Chronic>6 weeks[1].Chronic urticaria includes physical urticaria (cold, pressure, vibratory, UV light and others) and both chronic idiopathic urticaria (CIU) and autoimmune urticaria.[4] The autoimmune origin

is the most accepted hypothesis advanced to explain inappropriate activation and degranulation of mast cells in urticaria. This theory is supported by the clinical association of CU with various autoimmune disorders, the frequent detection of circulating autoantibodies, positive association with HLA subtypes DRB*04 and DQB1*0302 and therapeutic response to plasmapheresis and intravenous immunoglobulin[5] .An association between chronic spontaneous urticaria and autoimmune thyroid disease was first reported by Leznoff and Sussman[6] and confirmed subsequently by many others. The association is particularly strong at 30% for patients with a positive basophil histamine release test as a marker of functional autoantibodies.[7] there also appears to be a higher frequency of autoimmune disease in patients with autoimmune urticaria. The aim of this study to evaluate the association of autoimmunity in autologous serum skin test positive and negative chronic urticaria cases.

Material & Methods

This is a hospital based, observational comparative analysis done on 300 patients (150 patients in each group) in the Department of dermatology, venereology and leprosy**,** SMS hospital, Jaipur from March 2016 to October 2017.

Inclusion criteria

- Patients with chronic urticaria
- Patients willing to give written informed consent to participate

Exclusion criteria

- Urticaria < 6 weeks
- Patients on antihistaminics in past 2 days or on steroids or any other immunosupressive medications in past 2 weeks
- Pregnant or lactating women.
- Severely ill patients and Immunocompromised patients

Method of ASST

About 5 ml venous blood were collected in a sterile vacutainer and allowed to clot at room temperature for 30 minutes and centrifugated at 2000 rpm for 15 minutes 0.05 ml of autologous serum were injected intradermally using a 1 ml insulin syringe (30 gauge needle) to the right forearm 2 cm below the cubital fossa and similarly 0.05ml of 0.9% sterile normal saline (control) in the left forearm.

A serum induced erythematous weal with a diameter of 1.5 mm more than the saline induced response within 30 minutes would be taken as a positive test. Two groups were made in our study, Group I: ASST Positive and Group II: ASST Negative. All baseline routine investigations and autoimmune profile were done in both groups.

Statistical Analysis

Continuous data would be summarised in form of mean & SD. The difference in mean were analysed by using student ‘t’ test. Count data were expressed in form of proportion difference were analysed using chi square test. The level of significance was kept 95% for all statistical analysis.

Results

Our study showed that the mean age were 29.66 and 29.24 for ASST positive and negative group respectively but not statistically significant (P=0.765) (table 1). ASLO titer was positive in 20 (15%) subjects and 19 (14.4%) subjects in ASST positive and negative group respectively. The study groups did not differ significantly in relation to ASLO positivity (P>0.05) (table 2).

Our study showed that ANA was positive in 5 patients in ASST positive group, however difference was not

statistically significant (P>0.05) (table 3). The mean serum level of IgE in ASST positive group was higher (349.04IU/ml) as compared to ASST negative group (288.08IU/ml), but not statistically significant (P=0.193) (table 4). Similarly , no statistically significant difference found in rheumatoid factor (RF) among the two groups (table 5)

The present study showed that the Anti-TPO antibodies were positive in 54(40%) and 3(2.2%) patients in ASST positive and negative group respectively which were statistically significant in both groups (table 6) (P=0.001)

Discussion

Chronic urticaria (CU) is defined as urticaria persisting daily or almost daily for more than six weeks but the individual lesion does not remain for more than 24 hours.[8] The Pathophysiology of CU is not completely understood, although most agree that the central event is activation of cutaneous mast cells. The autoimmune origin is the most accepted hypothesis advanced to explain inappropriate activation and degranulation of mast cells in urticaria. During the last decade various studies have been done to gain insight into the pathogenesis of CU. 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.

Autologous serum skin test (ASST) is a simple *in-vivo* clinical test for the detection of basophil histamine releasing activity.[9] ASST may be used to distinguish between patients with and without circulating functional autoantibodies. This would be of value to diagnose autoimmune urticaria and to evaluate the effectiveness of immune-modulatory treatment. In this descriptive, comparative, observational study we evaluated the association between CU and autoimmunity for which we categorized the CU patients in autologous serum skin test(ASST) positive and negative group, and patients in both groups were evaluated for autoantibodies which included rheumatoid factor (RF), anti-sreptolysin-O (ASLO), anti-nuclear antibody (ANA), Anti thyroid peroxidase(Anti-TPO) and for IgE serum level .

In this study, majority of chronic urticaria patients were aged between 30-50 years (most commonly affected age group is 30-40 years). There was female preponderance with 52% patients being female and 48% male in ASST positive group, while in ASST negative group 57 % were female and 43% male. However difference was not statistically significant in both groups in relation to age and gender. In this study anti-TPO antibodies were positive in 54(40%) and 3(2.2%) patients in ASST positive and negative group respectively.

In 1983, a landmark study by Leznoff *et al*[6] showed significantly increased levels of anti-thyroid antibodies in CU patients compared to control population. Since then, the prevalence of positive thyroid autoantibodies ranged from 12 to 29% in patients with CU in different studies.[10-12] However study done Jindal R et al[13] found no statistically significant difference in thyroid antibodies in both groups.

In our study, we found comparatively higher frequency of thyroid antibodies(40%).).Apart from Anti-TPO antibody, ant- thyroglobulin antibody (anti-Tg) were also detected in CU in some studies.[14] We evaluated Anti-TPO antibody ,as it is established as a sensitive tool for the detection of early subclinical autoimmune thyroid diseases and identification of at-risk cases for autoimmune thyroid diseases.[15,16] Although a specific mechanism linking the development of thyroid disease and CU has yet to be firmly elucidated, it is widely thought that both diseases occur because of a propensity

within the patient to develop reaction to self. It has been hypothesized that thyroid disease may worsen urticaria through activation of the complement system.[17] Therefore, while it is hypothesized that thyroid disease and CU may coexist due to a patient's predilection for autoimmunity, thyroid disease may additionally exacerbate urticaria through direct mechanisms that result in complement activation. Contrary to this, the antithyroid IgG antibodies are not involved directly in the mast cell degranulation and pathogenesis of the chronic urticaria and only serve as indicator of autoimmunity.[11]

In our study we also observed that patients in ASST positive group with autoantibodies are more resistant to first line treatment which has been reported previously.[18] ANA was positive in 5(3.7%) patients in ASST positive group while in ASST negative group all 132 patients were ANA negative. ANA positivity in our patients was 3.7% which was comparable than 5% in normal individual. This was in contrast to the results of Kuo-Lung et al.[19] and Lenznoff et al.[20] who reported greater association of ANA and CU.

The mean serum level of IgE in ASST positive group was higher (349.04IU/ml) as compared to ASST negative group (288.08IU/ml), however difference was not statistically significant in our study. While Kessel *et al.*[21] and Abdel Azim et al.[22] showed significantly higher serum IgE level in ASST-positive patients[23], this is in contrast to the results of Huilan et al.[24] and Abd El-Azim and Abd El-Azim[25] who stated that a positive ASST result was more likely to be associated with significantly lower IgE levels than a negative ASST result, attributing it to IgE-anti-IgE immune complex formation reducing the amount of detectable free IgE in patients with anti-IgE autoantibodies.

In this study we observed that ASLO titer was positive in 20 (15%) patients and 19 (14.4%) patients in ASST positive and negative group respectively, though difference was not significant, which was comparable with reported by Parvaiz A. Rather et al.[26]

Table 1: Age distribution of study subjects

Age	Means (Yrs)	SD	P-value
ASST positive	29.66	11.88	0.765
ASST negative	29.24	10.87	

Table No. 2: Association between ASST and ASLO.

ASLO result	ASLO positive	ASLO negative	Total
ASST positive	20	112	132
ASST negative	19	113	132
Total	39	225	264
Chi-square value- 0.00		P-value-1.00	

Table No. 3: Association between ASST and ANA.

ANA result	ANA positive	ANA negative	Total
ASST positive	09	123	132
ASST negative	00	132	132
Total	09	255	264
Chi-square value- 7.36		P-value-0.007	

Table No. 4: IgE level

IgE level	Means	SD	P-value
ASST positive	349.04	459.55	0.193
ASST negative	288.08	277.98	

Table No. 5: Association between ASST and RF factor

RF result	RF positive	RF negative	Total
ASST positive	03	129	132
ASST negative	00	132	132
Total	03	261	264
Chi-square value- 1.34		P-value-0.246	

Table No.6: Association between ASST and Anti TPO

Anti TPO result	Anti TPO positive	Anti TPO negative	Total
ASST positive	54	78	132
ASST negative	03	129	132
Total	57	207	264
Chi-square value- 55.93		P-value-0.001	

Conclusion

Our study concludes that all patients with CU should be evaluated for ASST and thyroid auto- antibodies. These tests may show their utility in the management of resistant cases. Cases which are resistant to the first line treatment, may get benefit by the addition of mast cell stablizers or other immunosuppressive drugs.

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