



## TO EVALUATE THE ASSOCIATION BETWEEN CLINICAL PARAMETERS OF CHRONIC URTICARIA AND VARIOUS BIOMARKERS

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### ABSTRACT

**Introduction:** Causes of chronic urticaria (CU) remain obscure. Laboratory parameters or biomarkers can be a predictor of duration and severity of Urticaria.

**Objective:** The aim of this study was to evaluate the association between clinical parameters of chronic urticaria and various biomarkers.

**Methods:** A retrospective cross-sectional data of 134 patients of chronic urticaria seen in allergy-clinic, during recent 2 years span were collected. Demographic details, duration of the disease, urticaria activity score (UAS), Autologous serum skin test (ASST) and various autoimmune and inflammatory laboratory parameters were included.

**Results:** We found disease activity (UAS) was significantly associated with biomarkers, ASST (.044), CRP (.025) and ANA (.000). ANA positivity was significantly (.000) associated with duration of the disease.

**Conclusions:** The present study found association of chronic urticaria with inflammatory and autoimmune markers; hence it is important to monitor certain laboratory testings like, CRP, ESR, ANA, ASST, Thyroid auto antibodies, IgE and routine blood count to predict the disease duration, severity and to manage patients appropriately.

**KEYWORDS :** Urticaria; biomarkers; Autoimmunity; Inflammatory

### INTRODUCTION

The term chronic spontaneous urticaria (CSU) is used to describe those cases in which the cause could not be determined despite of intensive clinical and laboratory investigations. Autoimmune mechanisms have been proposed to cause some cases of CSU. This was supported by the observation that an intradermal injection of autologous serum (autologous serum skin test) elicited immediate wheal and flare response in 60% of patients with CSU (1). Later IgG autoantibodies directed against IgE or FCER1 receptor on IgE were demonstrated and were found to be the cause of autoimmune Urticaria (2). The autoimmune process in CSU overlaps with many other autoimmune diseases, most common amongst them is the autoimmune thyroid disease (3). The incidence of thyroid autoantibodies in patients with CU ranges from 6.5% - 57% (4, 5). Total IgE has been found to be raised in patients with CU. This is because of polyclonal activation of B cells in CU (6). Thus, autoimmune markers like antinuclear antibodies (ANA), rheumatoid factor (RF), anti-thyroid peroxidase antibodies (anti-TPO Ab), autologous serum skin test (ASST) and total IgE are important investigations in CSU. Characterization of inflammatory response - erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are essential for an insight into the pathophysiology of the disease as well as its activity, severity and diagnosis/management of infections and autoimmune diseases in the course of chronic Urticaria (7). Infections can cause urticaria by inducing molecular mimicry, hence identification and management of infections in patients of CU is essential (8).

### MATERIALS AND METHODS

We retrospectively evaluated 134 patients of chronic urticaria seen in allergy clinic of Department of Dermatology, Venereology and Leprosy at ABVIMS Dr. Ram Manohar Lohia Hospital, recent 2 years span after taking approval from institutional ethical board. Patients of acute urticaria (duration of urticaria < 6 weeks), physical Urticaria (excluded with proper history), urticarial vasculitis, children less than 12 years, pregnant and lactating women were excluded. Data were collected regarding, age, sex, disease duration, severity

and laboratory parameters. We used urticaria activity score (UAS) to assess severity of the disease (9). Autologous serum skin test (ASST) done for each patient by injecting intradermally of 0.1 ml each of autologous serum, saline (negative control) on the volar aspect of left forearm with a gap of 5 cm between each injection site. After 30 minutes the wheal formed at each injection site were measured at two perpendicular diameters (d1, d2) and the average of the two was calculated. ASST was considered to be positive if serum-induced wheal had a diameter (average of d1 and d2) of  $\geq 1.5$  mm as compared to the saline-induced wheal at 30 minutes (10). Various serologic autoimmune and inflammatory markers assessed by different methods including, antinuclear antibodies (ANA), rheumatoid factor (RF), thyroid autoantibodies-thyroperoxidase (anti-TPO < 50 IU/ml), serum total IgE (female < 250 IU/ml, male < 250 IU/ml) and C-reactive protein (CRP) assessed by ELISA. Thyroid function test (TFT) by chemiluminescence (Vitros Eci, Johnson and Johnson) and anti-streptolysin antibodies (ASO) by latex agglutination method. Complete haemogram and erythrocyte sedimentation (ESR), routine and microscopic examination of urine and stool examination for ova and cyst were done for each participant.

### STATISTICAL ANALYSIS

For demographic and other clinical variables we use descriptive statistics, using Mean  $\pm$  Standard Deviation and percentage (frequency). We compared between all clinical with laboratory variables by using ANOVA. Pearson correlation was used to find correlation of these lab and clinical variables. A p value of < 0.05 was considered as statistically significant. We used SPSS soft version 20.0.

### RESULTS

Of the 134 patients with chronic spontaneous urticaria 92 (68.7%) were female, 42 (31.3%) male with the average age of 35 year (14 yrs-72 yrs). The duration of the onset of disease was average 38 months (2 - 360 months). Urticaria activity score was found to be of moderate grade among 84 (62.7%), severe grade 31 (23.1%) and mild grade 19 (4.2%). Autologous serum skin test (ASST) was positive in 40 (29.9%). Among 40,

26(65%) were female and 14(35%) were male. Anti-nuclear antibodies and rheumatoid factors were found to be positive in 20(14.9%) of patients. Both ANA and RF were raised in only 3 patients (2.2%). Out of 20 rheumatoid factor and ANA positive patients, 12(60%) were female and 8(40%) male. ANA and ASST were positive in 10 (7.46%) cases. 31(23.5%) had risen anti thyroid antibodies. Serum IgE was significantly raised in 82(61.2%). Laboratory inflammatory markers ASO and CRP were positive in 11(8.2%) and 49 (36.6%) respectively. Routine stool and urine samples were showed 13(9.7%) and 31(23.1%) positive for cyst of giardia and bacteria respectively. ESR was raised among 32(25%) patients as shown in table 1, 2. There were no significant difference of all clinical and lab parameters in both sexes except ESR in female (p=.007), comparison to male. We found positive association of age with duration (p=.000), serum IgE (p=.025) and ESR (.044). The study showed positive association of CRP with UAS (.025) and raised count of total leucocytes (.025). Absolute eosinophil counts (AEC) was associated with raised TLC and UAS with statistical significant p value of .025 and .043 respectively. Raised ESR associated with ANA, Anti-TPO and positive stool test for giardiasis with significant p value.026, .024 and .027 respectively. All CU patients with RF positive were associated with raised serum IgE (.020) ANA positivity was significantly (.000) associated with duration of the disease, raised ESR (0.026) and UAS (0.000). Positive result of ASST was significantly correlated with UAS (.044) as shown in table 3. Angioedema was found in only 4(3%) person.

**DISCUSSION**

The present study has shown 68.7% female preponderance similar to previous studies (11). The mean age of the patients were 35.45 years which was comparable to the study done by George et al (13). Average duration of chronic urticaria was 38 months and CU patients with ANA positivity had prolonged duration (11). We found, elderly patients had prolonged disease-duration (.000) with raised value of ESR (.040) and serum IgE (.025). Although measuring ANA serves as a nonspecific marker of systemic autoimmunity, its relationship with CU is poorly understood. Nonetheless, positive ANA has been found to have some correlation with CIU severity and was strongly associated with refractoriness to antihistamines (14). Whereas in other study CU duration was associated clinical parameters such as severity and angioedema, and presence of both autologous serum test and anti-thyroid antibodies (15). In our study disease duration was associated with age, CRP ANA and ASST positivity. ASST was found to be positive in 40 patients (29.9%), these were associated with moderate to severe grade of urticaria (UAS). Some studies also showed severe clinical features in ASST positive CU than ASST negative(16), in contrast to the other study which did not found such association (17). Similar to most of the previous studies, our study was found positive correlation between CRP and severity of Urticaria (17, 18). This indicates that CRP levels reflect activity of disease and it may serve as a biomarker to monitor CSU patients. CRP positive individual also had raised total leukocytes counts (TLC). We found association of raised serum IgE with positive RF. RF were positive in 20(14.9%) patients all had raised serum IgE level. Earlier studies also found high titres of IgE in serum of rheumatoid arthritis (RA) (19, 20) patients but no increased prevalence of atopy (21, 22) rather decreased prevalence (23). De Clerck et al. found elevated IgE levels and IgE circulating immune complex in RA patients more frequently than in patients with allergic asthma and good correlation between skin IgE deposition and extra

articular manifestations of RA. In our studies we did not find any clinical severity in RF positive CU patients with raised serum IgE. We also did not found any correlation of thyroid autoantibodies to sex, duration, severity, ASST, ANA positivity in CU. Elevated ESR was seen in thyroid auto-antibodies positive patients (p=.024) similar to result found in other study (24), ANA positive, female and elderly individuals and patients associated with positive stool test for ova and cyst. Raised AEC were found to be associated with raised TLC and CU severity.

**CONCLUSIONS**

In our study we found, chronic urticaria was seen more commonly in female. Disease duration was prolonged in elderly and patients with autoimmunity. Disease severity was found to be associated with inflammatory marker-CRP positivity, peripheral eosinophilia and ANA, ASST positivity. Hence, it is important to monitor certain laboratory testings like, CRP, ESR, ANA, ASST, Thyroid auto antibodies, IgE and routine blood count to predict the disease duration and severity and to manage patients appropriately.

The limitation was that we have not covered the therapeutic part/response in our patients, no comparison with healthy control and also the sample size was not adequate to derive any final conclusion.

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**Table 1. Showing demographic and clinical profile**

Sex	Number of patients (%) (n=134)	Mean±SD
Males	42 (31.3%)	52.17+83.46
Females	92 (68.7%)	31.20+41.75
Age (years)		
Range	14-72	35.45±11.94
Duration(months)		
Range	2-360	37.77±58.61
Severity of urticaria (UAS7)		
Mild	19 (14.2%)	27.54±8.364
Moderate	84 (62.2%)	
Severe	31 (23.1%)	

**Table 2. Percentage of patients with positive inflammatory and autoimmune markers.**

Inflammatory markers	Positive (No. of patients, %) n=134	Autoimmune markers	Positive (No. of patients, %) n=134
ESR	32 (25%)	ANA	20 (14.9%)
CRP	49 (36.6%)	Anti- TPO Antibodies	31 (23.5%)
ASO	11 (8.2%)	ASST	40 (29.9%)
AEC	24 (17.9%)	RF	20 (14.9%)
TLC	7 (5.2%)	S. IgE	82 (61.2%)

ESR- Erythrocyte sedimentation rate, CRP-C-reactive protein, ASO- Antistreptolysin O, AEC- Absolute eosinophil count, Total leukocyte count  
ANA- Antinuclear antibodies, Anti-TPO- Anti thyroid peroxidase, ASST- Autologus serum skin test, RF- Rheumatoid factor

**Table 3. Significant correlation between various clinical and laboratory parameters.**

Inflammatory markers with demographic and autoimmune parameters		*P value	Autoimmune markers with demographic and inflammatory parameters		*P value	Demographic with autoimmune and inflammatory parameters		*P value
ESR	Stool for ova and cyst	0.027	ANA	Duration	0.000	Duration	ANA	0.000

ESR	Age	0.044	ANA	UAS	0.000	Age	ESR	0.044
ESR	ANA	0.026	ANA	ESR	0.026	Age	Duration	0.000
ESR	Anti- TPO antibodies	0.024	Anti TPO antibodies	ESR	0.024	Age	S. IgE	0.025
ESR	Sex (female)	0.007	ASST	UAS	0.044	Sex	ESR	0.007
CRP	UAS	0.025	RF	Serum IgE	0.020			
CRP	TLC	0.025						
AEC	UAS	0.043						
AEC	TLC	0.025						

\*p value significant below 0.05 level, ESR- erythrocyte sedimentation rate, CRP- C-reactive protein, UAS- Urticaria activity score, TLC- Total leukocyte count, AEC- Absolute eosinophil count, ANA-Antinuclear antibodies, ASST-Autologus serum skin test, RF- Rheumatoid factor

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