

Pattern of chronic urticaria and value of autologous serum skin test in Sohag Province, Upper EgyptReham Ezz El-Dawla El-Sharkawy¹, Wafaa Mohamed Abd-Elmaged², Doaa Anwar Ahmed³, Sahar Abo El-Fetoh Abdel-Wahed⁴

¹ Assistant Professor, Dermatology and Venereology Department, Faculty of Medicine, Sohag University, Sohag, Egypt

² Lecturer, Dermatology and Venereology Department, Faculty of Medicine, Sohag University, Sohag, Egypt

³ Resident at Dermatology Department, Sohag General Hospital, Sohag, Egypt

⁴ Assistant Professor, Clinical Pathology Department, Faculty of Medicine, Sohag University, Sohag, Egypt

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Abstract

Background: Chronic urticaria (CU) is a debilitating disorder with variable clinical course. It is characterized by hives occurring for at least 6 weeks, and is classified as spontaneous or inducible.

Objective: The aim of this study was to detect the pattern of CU, to study association between results of autologous serum skin test (ASST) and urticaria severity score (USS), and to detect serum levels of anti IgE receptors antibodies.

Methods: This study included all patients attending the Dermatology Outpatient Clinic, Sohag University Hospital, who were diagnosed as CU from April 2015 to March 2016. ASST and serum level of anti IgE receptor antibodies was assessed using ELISA. Data were analyzed by SPSS version 16, using descriptive statistics, Kruskal-Wallis and Mann-Whitney U test.

Results: A total of 108 patients with CU were included in the study. Females with mean age 33±12.4 years were more affected. A total of 58.3% complained of CSU, 6.5% physical urticaria and 35.2% mixed type of CU. According to USS, mild score represented 20.4%, moderate 46.3% and severe in 33.3%. ASST showed positive in 38% of patients. There was a statistically significant relation between ASST and USS and duration of CU. This indicates that more severe symptoms and prolonged duration of CU are observed in positive ASST (autoreactive type). In all, 91% of the anti IgE receptor antibodies positive patients had positive ASST.

Conclusion: In conclusion, chronic urticaria is not an uncommon disease in our locality which represented 1.13% of our patients. Urticaria severity score and duration of urticaria was higher in positive ASST patients and hence the autoreactive type.

Keywords: Severity score, Skin test, Urticaria

1. Introduction

Chronic urticaria (CU) is a skin disorder characterized by transient pruritic wheals that recur from day to day for 6 weeks or more. Females are affected nearly twice as often as males, and the peak age of manifestation of CU is 20-40 years (1). The incidence of CU has been estimated at 1.4% per year in the USA (2). It is divided into chronic spontaneous (CSU) and inducible urticaria (3), Chronic inducible urticaria is defined when a trigger can be identified (4). In CSU, the appearance of lesions is not triggered by consistent or identifiable factors, and it specifically excludes physical urticaria syndromes. It accounts for approximately two-thirds of all cases of CU. CSU is classified into 2 subtypes including chronic autoreactive and idiopathic urticaria (5). The most severe form of CU is autoreactive chronic urticaria (ACU) and it is associated with presence of circulating histamine-releasing autoantibodies, specifically directed against IgE high-affinity receptors (FcεRIα) that are present in the cytoplasmic membrane of mast cells and basophils or anti-IgE autoantibodies (6). The autologous serum skin test (ASST) can

Corresponding author:

Wafaa Mohamed Abd-Elmaged, Dermatology and Venereology Department, Faculty of Medicine, Sohag University, Sohag, Egypt.

Tel.: +20.1008813349; Fax: +20.934602963, E-mail: wafaa_Mohamed@med.sohag.edu.eg

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assess autoreactivity in ACU patients. It can be identified as mast cell-activating autoantibodies that act either indirectly through the release of mediators from cutaneous mast cells and a number of other cells, or act directly in the microvasculature of the skin (7). The test is a simple in-vivo clinical test which detects basophil histamine releasing activity (8). Autoreactive CU has been associated with autoimmune conditions, such as the presence of elevated thyroid autoantibodies, type 1 diabetes mellitus (9), rheumatoid arthritis, Sjogren syndrome, celiac disease, and systemic lupus erythematosus (10). Chronic idiopathic urticaria (CIU) is the CU with no obvious cause, patients with CIU do not have evidence of autoimmunity. There is persistent activation of mast cells, but the mechanism of mast cell triggering is unknown (11). The aim of this study was to detect the pattern of CU among the patients attending our outpatient clinic, also to study the association between the results of autologous serum skin test (ASST) and urticaria severity score (USS), and to detect serum levels of anti IgE receptors antibodies using ELISA.

2. Material and Methods

2.1. Study design and population

This cross sectional study included all patients attending the Dermatology Outpatient Clinic, Sohag University Hospital, who were diagnosed as CU from April 2015 to March 2016.

2.2. Selection criteria

The study included all cases of CU, both sexes, aged from 15-70 years old. Exclusion criteria were pregnant and lactating women, patients aged less than 15 and more than 70 years old, and patients complaining of angioedema without wheals and urticarial vasculitis.

2.3. Study steps

Complete history was taken from each patient: systemic symptoms and history of atopia, past history of similar condition or drug intake, family history, and autoimmune diseases. Urticarial severity was assessed for each patient using urticaria severity score. The severity score was divided into mild (≤ 5), moderate (6-10), and severe (>10) (12). General and dermatological examination was done for each patient, laboratory tests included complete blood count, liver and renal function, ESR, urine and stool analysis, total T3 and T4 level, helicobacter pylori antigen and antibody titer for hepatitis B and C virus. Autologous serum skin test was done. Patients were required to be off antihistamines treatment for at least 3 days and corticosteroids and other immunosuppressive drugs for 4 weeks before the study, to reduce the possibility of generating false-negative results (7). Venous blood samples of 5 ml were collected in sterile plain tubes without a clotting accelerator, and were allowed to clot for 30 min at room temperature. After 15 min centrifugation at 2000 rpm, samples of 0.05 ml of autologous serum and 0.9% sterile normal saline were separately injected intradermally into the volar aspect of the right forearm with a 5 cm gap between injection sites. Wheal and flare response was measured at 30 min. ASST was recorded as positive if a serum-induced wheal which was both red and with its diameter larger than a saline-induced response by ≥ 1.5 mm was seen at 30 min (8). To confirm the autoreactivity of CU, serum level of anti immunoglobulin E receptor antibody was assessed using ELISA method (Kit provided by Glory Science Co., Ltd, USA.CATALOG #: 12252), allowing for the in vitro quantitative determination of anti-IgE receptor antibody concentrations in serum of the patients.

2.4. Statistical analysis

Data were analyzed using SPSS version 16.0 (SPSS Inc., Chicago, Illinois, USA). The data were tested for normality using Kolmogorov-Smirnov, and Shapiro-Wilk tests which were significant indicating the use of non-parametric tests as data was not normally distributed. Chi-square test was used for comparison regarding qualitative variables. The non-parametric Mann-Whitney U test was used for comparing two quantitative variables. Kruskal-Wallis test was used for comparison between more than two quantitative variables. P-value ≤ 0.05 was considered significant.

2.5. Ethics

The study was submitted for approval by the Research and Ethical Committee at the faculty. Written informed consent was obtained from each patient.

3. Results

3.1. General findings

A total of 108 patients with CU were included in the study. They composed 1.13% of a total 9,600 patients who attended the dermatology clinic at our hospital from April 2015 to March 2016. The mean age of the patients was 33 ± 12.4 years. Eighty five patients (78.7%) were females, with male to female ratio at 1: 3.7. Their socio demographic characteristics were demonstrated in Table 1.

Table 1. Sociodemographic characteristics of the study group (n=108)

Socio demographic characteristics		n (%)
Age (year) (Mean \pm SD= 33 \pm 12.4)	15-20	18 (16.7)
	20-40	55 (50.9)
	40-60	32 (29.6)
	>60	3 (2.8)
Gender (Female/ male ratio = 3.7)	Female	85 (78.7)
	Male	23 (21.3)
Residence	Rural	56 (51.9)
	Urban	52 (48.1)
Marital Status	Married	74 (68.6)
	Single	28 (25.9)
	Widow	5 (4.6)
	Divorced	1 (0.9)
Special Habits	Smoker	11 (10.8)
	Non Smoker	97 (89.8)
Occupation	House Wife	67 (62)
	Manual Worker	21 (19.4)
	Officer	12 (11.2)
	Student	8 (7.4)

3.2. The characteristics of chronic urticaria

A total of 63 patients (58.3%) had CSU, seven patients (6.5%) had physical urticaria and 38 patients (35.2%) had mixed type of CU. The mean duration \pm SD was 3.1 \pm 3.87 years. In all, 57 of the patients (52.8%) had angioedema and wheals and 51 (47.2%) had wheals only. Only 7 of the patients (6.5%) were H pylori antigen positive but 5 of them (4.7%) had thyroid disease, 8 (7.4%) were hepatitis C positive, one (0.9%) was positive for hepatitis B surface antigen and a majority of 80 (74.1%) had normal laboratory findings, and urticarial symptoms were exacerbated in 35 (32.4%) due to NSAID intake patients. The most common aggravating factors for urticarial symptoms were stress 53 (49%), followed by sun exposure 28 (25.9%) and food 27 (25%).

3.3. Autologous serum skin test (ASST)

Regarding ASST, it was positive in 41 (38%) patients (Figures 1, 2). There was a statistically significant relation between ASST result and duration of the disease ($p=0.014$) as shown in Table 2. But no statistically significant relation between ASST and age of the patients or the type of CU ($p=0.403$, $p=0.081$ respectively).



Figure 1. Positive ASST.



Figure 2. Negative ASST.

Table 2. The relation of ASST to the duration of disease group (n=108)

Duration of disease	Positive ASST; n (%)	Negative ASST; n (%)	Total; n (%)
<1 year	6 (17.1)	29 (82.9)	35 (100.0)
1-5 years	23 (44.2)	29 (55.8)	52 (100.0)
5-10 years	6 (60)	4 (40)	10 (100.0)
≥10 years	6 (54.5)	5 (45.5)	11 (100.0)
Total	41 (38)	67 (62)	108 (100.0)
$\chi^2 = 10.65, p=0.014^*$			

* Chi square test

3.4. Urticaria severity score (USS)

With regard to USS, 22 (20.4%) of the patients had mild score, 50 (46.3%) moderate score and 36 (33.3%) severe score. The relation of USS to the positivity of ASST was statistically significant ($p=0.000$) as shown in Table 3.

Table 3. The relation of ASST to each score group (n=108)

The score	Positive ASST; n (%)	Negative ASST; n (%)	Total; n (%)
≤5 (mild)	0 (0)	22 (100)	22 (100.0)
6 to 10 (moderate)	12 (24)	38 (76)	50 (100.0)
> 10 (severe)	29 (80.6)	7 (19.4)	36 (100.0)
Total	41 (38)	67 (62)	108 (100.0)
$\chi^2 = 45.33, p=0.000^*$			

* Chi square test

3.5. Serum level of anti IgE receptor antibodies

The normal detection range of anti IgE receptor antibodies in the serum is 7-200 ng/ml. In the present study, those antibodies were searched for in 83 patients. It was found that 33 (39.8%) of those patients had positive antibodies but 50 (60.2%) had negative ones. The majority (90.9%) of the antibody positive patients had positive ASST compared to those who had negative ASST (9.1%), which was statistically significant ($p=0.000$). The mean of anti IgE receptor antibodies in the ASST positive group was more than that of the negative one, (28.72 ± 43.6 ng versus 2.79 ± 1.19 ng) that was highly significant ($p < 0.001$). But there was no statistically significant relation between the level of these antibodies and age of patients, type of CU and duration of the disease ($p=0.383$, $p=0.472$, and $p=0.212$ respectively).

4. Discussion and conclusions

Chronic urticaria (CU) is a skin disorder characterized by the recurrent appearance of wheals and/or angioedema for at least 6 weeks. CU is a heterogeneous disorder which includes chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIU) (13). Our study included 108 patients complaining of chronic urticaria. They represented 1.13% of the total of patients who attended the dermatology clinic at Sohag University Hospital from April 2015 to March 2016. This result is similar to that stated by Abd El-Azim and Abd El-Azim (7) that chronic urticaria affected up to 1% of the general population. Eighty five patients (78.7%) were females, with male to female ratio at 1: 3.7. So there is a female predominance similar to previous studies (8, 14). The reasons for these sex-related differences are not completely understood. A possible explanation may be the autoimmune nature of the disease, at least in a subgroup of patients with CSU (15). In the current study the mean age of the patients is 33 ± 12.4 years. This result is comparable to a study done by Lee et al. (16) from Taiwan who found that the mean age was 31.8 ± 10.4 . Another study by Choi et al. (17) from Korea found that the mean age is older and was 40.8 ± 10.6 years. The peak age of chronic urticaria patients is between 20 and 40 years in most studies. This means that patients are primarily affected during important years of their working age. The present study showed that mean of duration of chronic urticaria is 3.1 ± 3.87 years. This is in consistent with a study done by Abd El-Azim and Abd El-Azim (7) who found the mean duration of chronic urticaria was 2.2 ± 2.5 years. In contrast to a study done by Heng et al. (18), in which the mean duration of complaint ranged from 1.5 months up to 10 years. This means that duration of chronic urticaria varies widely among different populations and from one person to another in the same population. In the present study 52.8% of the patients have associated angioedema that is near to the finding of Vikram Kumar et al. (19) who found that 66% of the patients had associated angioedema. This was higher than other studies (7, 8). These differences indicate variation of incidence of angioedema that is associated with chronic urticaria of unknown cause. In this study, 63 of the patients (58.3%) complained of CSU, 7 (6.5%) of the patients complained of physical urticaria and 38 (35.2%) complained of mixed type of chronic urticaria. In another study done by Ue et al. (20), the percentages were 23.3%, 27.4%, and 40.3% respectively. Dermographism was present in 39 patients (36%) either alone or in association with chronic spontaneous urticaria that is concurrent with a study done by Abd El-Azim et al. (21). This explains that symptomatic dermographism represents the most common type of physical chronic urticaria. Ten percent of the patients in this study had an urticarial wheal concomitantly with atopic symptoms. These were suspected of being an IgE-mediated mechanism. Previous study done by Vichayanond et al. (22) revealed little evidence to suggest that allergy is an important factor in CU. However, allergy is more important in acute urticaria than chronic urticaria. Various infections have been reported to be the associating factors of CU including parasitic infection, hepatitis and *H. pylori* infection. In this study, 6.5% of the patients were positive for helicobacter pylori antigen, which is in contrast to a study done by Yadav et al. (23) from India, in which 70.5% of patients were positive for this finding. Such different results could be explained by differences in the antigenicity or biological activity of the bacteria (HP) in different areas, with different socio-economic and genetical patterns of the host population (24). *H. pylori* can have an indirect involvement in the etiology of CU, by reducing the immune tolerance and inducing the formation of autoantibodies, including the production of autoantibodies to anti-Fc ϵ RI α (25). In this study, 7.4% and 0.9% of the patients are hepatitis C and hepatitis B positive respectively in contrast to a study done by Bhatt (26) in which 2.8% of the patients were seropositive for HBsAg and none for the anti-HCV. Another study done by Malik et al. (27) showed that 1.1% of patients of chronic urticaria had anti-HCV antibody. Parasitic infestation was present in 4.6% of our patients. This was less than that of a study done in 2012 by Dilek et al. (28) in which 38.8% of the patients had parasitic infestation in association with chronic urticaria. In previous studies, the urticarial symptoms did not improve or were not completely cured after treatments of parasitic infestations, this implied that these might be co-incident symptoms. In the current study, five patients (4.7%) had thyroid disease. Confino-Cohen et al. (10) reported a higher percentage of thyroid problems in their study (9.8%). Both indicate the association of chronic urticaria to thyroid disease. This may explain the coexistence of autoantibodies in both (anti-thyroid peroxidase antibodies and IgE receptor antibodies) because of B-cell hyperreactivity.

Food has been implicated in 19 patients (17.59%) and the most common aggravating food was seafood, preserved and salty food. Food allergy and pseudoallergic reactions to food additives may have a role in some patients. Drugs account for a minority of chronic urticaria. However, it is common to see exacerbation of chronic urticaria caused by medication (29). In our study urticarial wheals and symptoms were exacerbated in 32.4% of the patients following the intake of non-steroidal anti-inflammatory drugs (NSAID). This is coincident with Sussman et al. (30) stating that up to 30 to 50% of CSU patients have exacerbations associated with NSAID ingestion. This could be due to a direct action of these drugs on mast cell degranulation as a result of inhibition of the cyclo-oxygenase pathway, which causes enhanced production of leukotrienes. In the current study, 80 (74.1%) of the patients have normal laboratory investigations. The causes of CU still could not be identified. This is similar to the study of Kozel et al. (31) who

suggested that there is no need for routine laboratory investigation, and history is the most important factor in identifying the causes of CU. The urticaria severity score was divided into three groups: mild (≤ 5), moderate (6-10), and severe (>10) with a total mean \pm SD of 8.6 ± 3.31 . In the present study, about half of the patients (46.3%) showed moderate score, (20.4%) of the patients had mild score, and (33.3%) had severe score. This is consistent with another study done by Al-Hamamy et al. (12) in which about half of their patients showed moderate USS. However, this is in contrast to the results of Toubi et al. (32) who noticed that about half of their patients showed severe USS. These different results may be due to difference in severity of chronic urticaria among different people. In this study the frequency of ASST positive patients among patients with CU was 38%. Those were consistent with other studies done by Asero et al. (33) who found that 35% of their patients had a positive ASST. A subsequent study done by Caproni et al. (34) reported that prevalence of ASST positivity in patients of chronic urticaria varies from 34% to 67%. Those are a subset of patients with CU who have functional antibodies against the high affinity IgE receptor, or less commonly IgE. The prevalence difference according to the ethnic group of population suggests a genetic background for the disease (7). This study showed longer duration of chronic urticaria in patients with positive ASST. This is similar to that found in a study done by Abd El-Azim et al. (21). This could be explained by the difficulty in controlling chronic autoimmune urticaria. In contrast to this finding, George et al. (8) and Vikram Kumar et al. (19) found no significant difference in the duration of the disease between positive and negative ASST patients. A positive ASST has been associated with prolonged disease that is poorly responsive to routine therapy. One important advantage of ASST is to promote more tailored prognostic counseling. Hence, ASST is considered as a bedside clinical test which can detect the presence of autoimmunity in patients with CU (8). Nowadays, ASST is used to determine the need of autohemotherapy in treatment of some types of autoimmune chronic urticaria in the patients with positive one. There was insignificant difference between ASST positive and negative groups regarding age and the type of chronic urticaria. This finding was in agreement with that reported by Kulthanan et al. (29). Also in this study, the relationship between severity of symptoms (USS) and the positivity of the ASST was done. There was a highly statistically significant relation between severity of USS and positivity of ASST, indicating that chronic autoreactive urticaria patients have more severe symptoms that could not be controlled easily. This agrees with a study done by Caproni et al. (34) reporting that ASST positive patients had more widespread lesions and significantly more severe pruritus and systemic symptoms. This is in contrast to a study done by Al Hammamy et al. (12) and Lee et al. (16) showing that there were no statistically significant difference between ASST and the urticaria severity score. Serum anti IgE receptor antibody level was significantly higher in the ASST positive group in which 90.9% of the positive antibodies patients had positive ASST. There was a highly statistically significant relation between those antibodies and their mean \pm SD to the positive ASST patients ($p=0.000$). This explains the autoimmune nature. It is not affected by age of the patients, type, or duration of chronic urticaria. This result matched with other studies done by (21, 35) who found that serum IgE level was significantly increased in an ASST positive group in comparison to an ASST negative group. In conclusion, chronic urticaria is not an uncommon disease in our locality which represented 1.13% of our patients. Urticaria severity score and duration of urticaria was higher in positive ASST patients and hence the autoreactive type.

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Conflict of Interest:

There is no conflict of interest to be declared.

Authors' contributions:

All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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