

Pattern of chronic urticaria in Sohag University Hospitals

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Abstract

Background: 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).

Objective: To study the pattern of chronic urticaria among the patients attending dermatology outpatient clinic in Sohag University Hospitals and to study the association between the results of autologous serum skin test (ASST) and urticaria severity score (USS) and to detect serum level of anti IgE receptors antibodies using ELISA.

Results: ASST was positive in 41 (38 %) patients and there was a statistically significant relation between ASST result and duration of the disease (p value 0.014). 22 (20.4%) of the patients had mild score, 50 (46.3%) had moderate score and 36 (33.3%) had severe score. The relation of USS to the positivity of ASST was statistically significant (p value 0.000). The mean of anti IgE receptor antibodies in ASST positive group was more than that of those negative ones that was highly statistically significant (P value 0.000).

Conclusion: ASST remains a baseline diagnostic test for CAU. Patients with CAU had more frequent attacks and longer duration than other types of chronic urticaria.

Introduction

Chronic urticaria is a skin disorder characterized by transient pruritic wheals that recur from day to day for 6 weeks or more (1). Females are affected nearly twice as often as males, and that the peak age of manifestation of CU is 20–40 years (2). The incidence of CU has been estimated at 1.4% per year in USA (3). The current European Academy of Allergy and Clinical Immunology (EAACI), Global Allergy and Asthma European Network (GA2LEN), European Dermatology Forum (EDF) and World Allergy Organization (WAO) guidelines for urticaria recommend that chronic urticaria is then divided into its two primary subgroups according to whether symptoms occur spontaneously (chronic spontaneous urticaria) or are induced by a

demonstrable stimulus (chronic inducible urticaria) (4).

1) **Chronic inducible urticaria:**

Inducible CU is defined when a trigger for CU can be identified. There are many types including, symptomatic dermographism, cold urticaria, cholinergic urticaria, delayed pressure urticaria, solar urticaria, vibratory urticaria, aquagenic urticaria and contact urticaria (5).

2) **Chronic spontaneous urticaria:**

It refers to CU in which appearance of lesions is not triggered by consistent or identifiable factors, and it specifically excludes the physical urticaria syndromes (6). It accounts for approximately two-thirds of all cases of chronic urticaria (7). CSU is classified into 2 major subtypes including chronic autoreactive urticaria

and chronic idiopathic urticaria(8).

a-Autoreactive chronic urticaria (ACU):

Autoreactive chronic urticaria (ACU) is considered to be the most severe form of chronic urticaria(9). About 50% of the cases of chronic urticaria are considered autoreactive diseases, due to the presence of circulating histamine-releasing autoantibodies, especially directed against IgE high-affinity receptors (FcεRIα) present in the cytoplasmic membrane of mast cells and basophils or anti-IgE autoantibodies(10).

b-Chronic idiopathic urticaria (CIU):

Chronic idiopathic urticaria (CIU) is defined as the occurrence of daily, or almost daily, wheals and itching for at least 6 weeks, with no obvious cause (11). Patients with chronic idiopathic urticaria do not have evidence of autoimmunity. In this form of urticaria, there appears to be persistent activation of mast cells, but the mechanism of mast cell triggering is unknown (12).

Several etiologic factors have been associated with CU throughout history: thyroid diseases, pseudo-allergens, actual allergens, Helicobacter pylori infection, other infections/infestations and autoimmunity/ autoreactivity(10).

Diagnosis of chronic urticaria:

It is necessary to obtain a thorough history, including all possible eliciting factors, and to identify the significant aspects of the disease. These parameters are as follows: age of patients at presentation, age of patients at onset of urticaria, urticaria severity score, duration of the disease in months, duration of each wheal in hours, frequency of attacks per week, distribution of wheals, interference of the disease with daily activities, presence of angioedema, interference of the disease with sleep, presence of family history of chronic urticaria, presence of personal and/or family

history of atopy, and presence of personal and/or family history of autoimmune diseases and medications (NSAIDs, hormones, laxatives, immunizations); and observed correlation with food and stress(13).

Physical examination should include identifying and characterizing any current lesions, testing for dermatographism (hives induced by rubbing intact skin), and checking for signs of systemic illness (including recurrent fever, weight loss, and joint symptoms) (14). Routine hematological tests, including complete blood count, liver function tests, renal function tests, the determination of erythrocyte sedimentation rate, and C-reactive protein levels may be considered. Testing for Helicobacter pylori. Screening for thyroid autoimmunity by T3, T4 and TSH level, stools for parasites and urine analysis. When history suggests a physical urticaria, challenge testing with physical stimuli may be considered. The ASST is the only generally available test to screen for auto-antibodies against either IgE or the high-affinity IgE receptor (15).

2- Aim of the work:

The aim of this study is to:

- 1- Study the pattern of chronic urticaria among the patients attending dermatology outpatient clinic in Sohag University Hospitals.
- 2- And to study the association between the results of autologous serum skin test (ASST) and urticaria severity score (USS).
- 3- And to detect serum level of anti IgE receptors antibodies using ELISA.

3-Patients and methods:

This study included patients complaining of chronic urticaria (those having recurrent episodes of wheals with or without angioedema of at least 6 weeks) who attended Dermatology Outpatient Clinic at Sohag University Hospitals from April 2015 to March 2016. The study was submitted for approval by Research and Ethical

committees at Faculty of Medicine, Sohag University. A written informed consent was taken from each patient. The inclusion criteria was all cases of chronic urticaria, both sexes, those aged from 15-70 years old. The exclusion criteria was pregnant and lactating women, those aged less than 15 and more than 70 years old, patients complaining of angioedema without wheals and urticarial vasculitis.

The study was submitted for approval by Research and Ethical committees at Faculty of Medicine, Sohag University. A written informed consent was taken from each patient. Urticarial severity was assessed for each patient using urticaria severity score. The severity score was divided into three groups: mild (less or equal 5), moderate (6-10), and severe (more than 10) (13).

Table(I):Urticaria severity score (13)

Parameter	Score
Frequency of attacks: (Days per week)	
1-2 days	1
3-5 days	2
>5 days	3
Duration of each wheal:	
<1 hour	1
1-6 hours	2
6-36 hours	3
Distribution of wheals:	
Face and extremities	1
All over the body	2
Interference with sleep:	
No	0
Yes	2
Interference with activities:	
No	0
Annoying	1
Abstinence from work	2
Associated angioedema:	
Eyelids, lips, or hands	1
Any 2 of above	2
All of them	3

Autologous serum skin test (ASST) was done. Patients had to be off antihistamines for at least 3 days (long-acting antihistamines for 7 days) and corticosteroids and other immunosuppressive drugs for 4 weeks before the study to reduce the possibility of generating false-negative results (15).

Samples of 5 ml of venous blood were collected in sterile plain tube without a clotting accelerator and allowed to clot

at room temperature for 30 min. After centrifugation at 2000 rpm for 15 min, 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 gap of 5 cm between injection sites. Wheal and flare response was measured at 30 min. ASST was documented to be positive if a serum-induced wheal which was both red and had a diameter bigger

than a saline-induced response by ≥ 1.5 mm was seen at 30 min (16).

To confirm the autoreactivity of chronic urticaria, serum level of anti immunoglobulin E receptor antibody were assessed using ELISA method. Using Anti IgE receptor antibody kit allowing for the in vitro quantitative determination of anti-IgE receptor antibody concentrations in serum of the patients.

Statistical analysis:

Data was analyzed using SPSS computer program version 16.0. Qualitative data were presented as numbers and percentages. Quantitative

data were expressed as means \pm standard deviation, median and range. The data were tested for normality using Kolmogorov–Smirnov test and Shapiro-Wilk test which were significant indicating the use of non parametric tests as data wasn't normally distributed. Chi-square (χ^2) test was used for comparison regarding qualitative variables. The non parametric Mann–Whitney test was used for comparing two quantitative variables. Kruskal–Wallis test was used for comparison between more than two quantitative variables.

Results

Autologous serum skin test (ASST):

As regard ASST, it was positive in 41 (38 %) patients and negative in 67 (62%) as shown in table 1 and figure 1. There was a statistically significant relation between ASST result and duration of the disease (p value 0.014). But no statistically significant relation between ASST and age of the patients or the type of chronic urticaria (p value 0.403, 0.081) respectively.

Table 1: The autologous serum skin test (ASST) in the study group

The autologous serum skin test (ASST)	No.	%
Negative	67	62.0
Positive	41	38.0
Total	108	100.0



(a)

(b)

Figure 1: (a) Positive ASST, (b) Negative ASST.

Urticaria severity score (USS):

In our study, 22 (20.4%) of the patients had mild score, 50 (46.3%) had moderate score and 36 (33.3%) had severe score. The relation of USS to the positivity of ASST was statistically significant (p value 0.000) as shown in table 2.

Table 2: The relation of ASST to each score group (N. = 108)

The score	Positive ASST No. (%)	Negative ASST No. (%)	Total No. (%)
≤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*	

P- value was calculated by Chi square test.

Serum level of anti IgE receptor antibodies:

The normal detection range of anti IgE receptor antibodies in the serum is 7 ng/ml- 200 ng/ml. In the present study, those antibodies were searched for in 83 patients. Thirty three (39.8%) of those patients had positive antibodies but 50 (60.2%) had negative ones. Thirty (90.9%) patients of the antibody positive patients had positive ASST that was statistically significant (p value 0.000) as shown in table 3. The overall mean ± (SD) of anti IgE receptor antibodies in ASST positive and negative patients were 28.72 ± (43.62), 2.79 ± (1.19) ng/ml respectively. The mean of anti IgE receptor antibodies in ASST positive group was more than that of those negative ones that was highly statistically significant (P value 0.000).

Table 3: Anti IgE receptor antibodies in positive and negative ASST patients (N. =83).

Anti IgE R antibodies	Positive ASST No. (%)	Negative ASST No. (%)	Total No. (%)
Positive anti IgE R antibody	30 (90.9)	3 (9.1)	33 (39.8)
Negative anti IgE R antibody	11 (22)	39 (78)	50 (60.2)
Total	41(49.4)	42 (50.6)	83 (100.0)
$\chi^2 = 96.8$		P = 0.000	

P- value was calculated by Mann–Whitney test.

Discussion

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 and includes

chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIU) (17). Chronic autoreactive urticaria is a distinct subgroup of CU where its recognition

has facilitated better understanding of persistent chronic spontaneous urticaria. These patients have autoantibodies against alpha chain of IgE receptors of mast cells and basophils (18).

Our study included 108 patients complaining of chronic urticaria. They represented 1.13% of the total of patients who attended dermatology clinic at Sohag University Hospitals from April 2015 to March 2016. Eighty five (78.7%) patients were females and the male to female ratio is 1: 3.7. The reasons for this 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 (19). The present study showed that mean of duration of chronic urticaria is 3.1 ± 3.87 years. This is in consistent with another study (15). In contrast to another study (20) 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 person to another in the same population.

Sixty three of the patients (58.3%) in this study complained of CSU, seven (6.5%) of the patients complained of physical urticaria and 38 (35.2%) complained of mixed type of chronic urticaria. In another study (21), the percentages were 23.3%, 27.4%, 40.3% respectively. 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 studies (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, This is in contrast to a previous study (23) 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).

In the current study, five (4.7%) of the patients had thyroid disease. (25) reported higher percent of thyroid problems in their study (9.8%). Both indicates 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. Drugs account for a minority of chronic urticaria. However, it is common to see exacerbation of chronic urticaria caused by medication (26). 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 previous study (27). 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 our study, USS showed that 22 (20.4%) of the patients had mild score, 50 (46.3%) had moderate score and 36 (33.3%) had severe score. These results are near to the results of previous study (28) and in contrast to another one (13). Those different results may be due to different in severity of chronic urticaria among different people.

In this study the frequency of ASST positive patients among patients with CU was 38%. Those was in

compatible with previous study(29). Subsequent studies (30) and(31) 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 (15). 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 studies (32) and (31) and in contrast to other studies(13) and (19).

Serum anti IgE receptor antibody level was significantly higher in ASST positive group in which 90.9% of the positive antibodies patients were having 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. In other studies(33)and (21)there was a significant relation between elevated total IgE levels and patients with positive ASST.

6- Summary and conclusion:

In conclusion, Chronic urticaria is not uncommon disease. It has high incidence in females. Its severity varies according to its type. The autoimmune type is the most severe one and the longer in duration where ASST can indicate it in a high degree.

7- Recommendation:

Larger community based studies are needed to detect prevalence of chronic urticaria in populations, serum IgE level is needed to be assessed in all patients with chronic urticaria, thyroid

anti-microsomal and anti-peroxidase antibodies should be assessed in CU patients and larger studies with application of autohemotherapy are needed for patients with positive ASST.

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