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Individual and Laboratory Indices of 210 Patients with Chronic Urticaria with or without Angioedema Referred to the Asthma and Allergy Clinic of Ahvaz in 2015-2018

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ABSTRACT

BACKGROUND AND OBJECTIVE: Chronic urticaria is a common skin condition that is manifested with erythematous or white edema, itching, and transient dermis with or without angioedema. Due to insufficient knowledge of the etiology of many of these chronic lesions, this study was performed to investigate some factors related to individual and laboratory indices of patients.

METHODS: In this descriptive study, 210 patients (154 females and 54 males) with chronic urticaria referred to Asthma and Allergy Clinic of Ahvaz from September 2015 to February 2019 were evaluated. Routine tests were performed for all patients including blood cell count, antinuclear antibodies, thyroxine and thyroid stimulating hormones, anti-thyroperoxidase (TPO) and anti-thyroglobulin (Tg) antibodies, glutamate-oxaloacetate transaminase (GOT) and glutamate-pyruvate transaminase (GPT) enzymes, autologous serum skin test and stool test.

FINDINGS: Of all patients, 166 (79%) had physical urticaria, 125 (59.5%) had atopy and 158 (75%) had angioedema. Autologous serum skin test with a frequency of more than 74.28% was positive in patients. Except for 3 patients (1.42%) with low serum levels of thyroid stimulating hormone and normal thyroxine (mild hypothyroidism) and 49 patients (23.33%) with abnormal increase in anti-thyroperoxidase and anti-thyroglobulin serum antibodies, the rest of the subjects (75.23%) were healthy. The results of anti-nuclear antibody and stool tests were also generally normal.

CONCLUSION: Based on the results of this study, in order to diagnose patients with chronic urticaria with or without angioedema, it is necessary to perform autologous serum skin test and thyroid function tests along with detailed clinical examinations.

KEY WORDS: *Chronic Urticaria, Autologous Serum Skin Test, Thyroid Function Tests.*

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Introduction

Urticaria is a common skin disease with erythematous or white, itching, non-pitting oedema, and transient oedema of superficial layers to the dermis layer of the skin with or without angioedema (severe swelling in the hypodermis layer of the skin and mucous membranes), manifested by dilation of arterioles, increased blood flow, and swelling of the skin (1). Manifestations of urticaria that usually occur twice a week with an interval of at least 6 weeks or more are called chronic urticaria, and are classified into different subtypes of physical, chronic or spontaneous idiopathic, and urticarial vasculitis (2). Although there is a possibility and risk of urticaria in any age group and any gender, it is more common among women and the age range of 20 to 40 years (3).

According to available reports, the etiology of chronic urticaria is multi-causal and is divided into two categories: autoimmune and idiopathic causes (4). A study found that 15% of patients with chronic urticaria also suffer from thyroiditis with thyroid autoimmunity and in most people with normal functioning of thyroid, one of the causes of chronic urticaria can be the presence of anti-thyroid antibodies (5). Other important confirmed factors include dietary factors, medications such as acetyl salicylic acid, helicobacter pylori infections, atopy, indigestion, collagen and vascular diseases, and psychosocial stress (6, 7).

The exact pathophysiology of urticarial lesions, especially its chronic idiopathic subtype, is still not definitively agreed upon, but it has been reported that nutritional, medicinal, and infectious reactions (rarely) can be the potential and stimulating causes of disease (8). About one-third of patients with severe chronic urticaria have also been shown to have average platelet volume, positive rheumatoid factor, and anti-nuclear antibodies in laboratory tests (9, 10). There is also a positive relationship between the prevalence of chronic urticaria and the high risk of other autoimmune diseases and the increase in basophils-activating autoantibodies in this group of patients (11).

According to the results of most researchers, the pathogenesis of chronic urticaria depends in the first place on being aware of other comorbidities and physical causes of the disease and in the second place on finding the causes and aggravating factors of the disease (12-18). There are no specific laboratory tests, but efforts to find relevant laboratory evidence can be somewhat helpful in determining the etiology of the disease. The aim of this study was to further investigate some related and aggravating factors of the disease by measuring individual and clinical indices and changes in laboratory tests in patients with chronic urticaria referred to the Asthma and Allergy Clinic in Ahvaz, Khuzestan province, southwestern Iran.

Methods

This descriptive study was approved by the ethics committee of Ahvaz Jondishapur University of Medical Sciences with ethics code IR.AJUMS.HGOLESTAN.REC.1398.030, and was conducted on 210 patients with chronic urticaria referred to the Asthma and Allergy Clinic located in Sinuhe complex in Ahvaz from September 2015 to February 2019.

Inclusion criteria were based on the information in the records of patients referred to the clinic with a definite diagnosis of chronic urticaria by a dermatologist on this date. Their information included personal information, age (year), gender (male/female) and history and clinical examination including the duration of the disease, type of disease (month) and clinical signs of dermatitis such as pruritus, urticarial lesion, presence or absence of physical subtype, with or without angioedema, and presence or absence of atopy, along with laboratory tests such as complete blood cell count (lymphocytes, neutrophils, eosinophils, monocytes, basophils [cells per cubic millimeter]), platelets (cells per milliliter), hemoglobin (grams per deciliter), hematocrit (percentage), anti-nuclear antibodies (positive/negative), thyroid function indices (mIU/L) (thyroxine, thyroid stimulating hormone, anti-thyroperoxidase antibody, anti-thyroglobulin antibody), liver parameters (U/L) (glutamate-oxaloacetate transaminase and glutamate-pyruvate transaminase enzymes), stool test (positive/negative in terms of parasitic infection), and autologous serum skin test (positive/negative in terms of autoantibodies against the IgE receptor of mast cell).

Patients with acute urticarial lesions (less than 1 to 6 weeks), use of medications, concomitant presence of cardiovascular disease, metabolic diabetes and other abnormalities of the internal organs, occurrence of uncommon clinical symptoms such as fever, raised patches of skin due to subcutaneous bleeding, enlarged viscera and swollen lymph nodes were excluded.

Quantitative variables are reported as mean and standard deviation and qualitative variables are reported as number (percentage). The normality of quantitative variables was assessed using the Shapiro-Wilk test. Chi-square test (or Fisher's exact test) was used to examine

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the relationship between qualitative variables whereas independent t-test or its non-parametric equivalent (Mann-Whitney test) was used to compare quantitative variables between two independent groups (male/female). Data were analyzed using SPSS software version 22 and $p<0.05$ was considered significant.

Results

In this study, 210 people with chronic urticaria in the age range of 4-66 years were studied. The mean age of the subjects was 35.69±11.78 years. The highest number of people based on gender belonged to the female group with 154 people (73.33%) compared to the male group which included 56 people (26.71%) (Table 1). The average duration of the disease was 45 months for all individuals, with individuals over 40 years having the highest duration of (34.4 months) and individuals under 10 years having the lowest duration of the disease (8 months). Of all patients, 173 (82.3%) had physical urticaria, 132 (62.8%) had atopy and 165 (78.5%) had angioedema (Table 1).

Table 1. Individual and clinical characteristics of the patients in all samples and by gender

Variable	Total samples Number(%)	Females Number(%)	Males Number(%)	P-value
Age group				
4-10	5(2.4)	3(3.6)	2(1.9)	
11-20	10(4.8)	6(3.9)	4(7.1)	
21-30	58(27.6)	45(29.2)	13(32.2)	0.641 [a]
31-40	76(36.2)	56(36.4)	20(35.7)	
41-50	36(17.1)	28(18.2)	8(14.3)	
51-66	25(11.9)	16(10.4)	9(16.1)	
Having Physical urticaria				
Yes	173(82.2)	122(81.3)	44(83)	0.839
No	37(17.8)	27(18.7)	9(17)	
Having Angioedema				
Yes	158(61.6)	123(62)	35(60.4)	0.021
No	78(22.2)	57(18)	21(34)	
Having utopia				
Yes	125(81.8)	93(81.3)	32(83)	0.870
No	78(38.4)	57(38)	21(39.6)	
Result of anti-nuclear antibody test [1]				
Positive	11(7.8)	9(5.7)	2(8.5)	>0.99
Negative	129(91.5)	97(91.5)	32(91.4)	
Autologous skin condition [2]				
Positive	140(72.2)	108(77.1)	32(59.3)	0.019
Negative	54(27.8)	32(22.9)	22(40.7)	
Stool test result				
Positive	2(1.8)	2(2.4)	0(0)	0.413
Negative	3(2.7)	3(3.6)	0(0)	
Normal	106(95.5)	78(94)	28(100)	
Total urticaria severity score (Mean±SD)	15.46±2.12	15.63±2.15	15.12±1.67	0.026 [b]

[1] ANA: Anti-Nuclear Antibody, [2] ASST: Autologous Serum Skin Test.

[a] Chi-squared test

[b] Mann-Whitney test

Evaluation of white blood cells showed that the mean value in all patients was 7.78±2.21, of which 15 (6.19%) were above and 6 (1.42%) were lower than normal range. Regarding other hematological indices, it was found that in neutrophils 54 (25.71%) and 19 (9.04%) patients, lymphocytes 36 (17.14%) and 27

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(12.85%) subject, eosinophils 14 (6.66%) and 37 (17.61%) and monocytes 21 (10%) and 14 (6.66%), respectively above and below the normal range of the index. Regarding basophil factor, only 97 patients (46.19%) were below the normal range. The mean levels of serum hemoglobin and hematocrit in all patients were 39.68±7.46 and 12.85±1.45, respectively, and hemoglobin levels decreased in 31 cases (14.76%) and hematocrit levels decreased in 35 cases (16.66%). In addition, both hemoglobin and hematocrit indices were significantly different between the two genders (p<0.001). Decreased and increased platelet counts were observed in 5 patients (2.38%) and 7 patients (3.33%), respectively. Three patients had decreased TSH and normal T4 (1.42%), indicating mild hypothyroidism in this number of patients, while the rest (207 patients [98.57%]), had normal thyroid function. Increase in anti-thyroglobulin antibody levels was observed in 20 patients (9.52%) and increase in anti-TPO antibody levels was observed exclusively in only 22 patients (10.47%). 7 patients (3.33%) also had an abnormal increase in both antithyroid antibodies, and a total of 49 patients (23.33%) had antithyroid antibody disorder. In the evaluation of the liver panel, i.e., the functional activity of liver enzymes SGOT and SGPT, it was observed that 3 patients (1.42%) had an increase in serum SGOT level and two cases (0.95%) also had an abnormal increase in serum SGPT. Only in one patient (0.47%), both enzymes had increased functional activity and overall, 6 patients (2.85%) with chronic urticaria had hepatic hypertransaminasemia. On the other hand, serum changes of SGOT and SGPT were significant between both genders (p<0.001) (Table 2). The frequency of ANA positive was observed in 11 patients (5.23%) and the rest of the population (199) (94.76%) were ANA negative. ASST results also showed that almost the majority of patients, i.e., 156 (74.28%) were positive. There was a significant difference between the two genders in terms of Total Symptom Score (TSS) (p=0.026). Stool test was positive in only 2 patients (0.95%), 205 (97.61%) were normal, and 3 (1.42%) were negative (Table 1).

Table 2. Descriptive indices of variables related to complete blood cell count, thyroid and liver function in patients with chronic urticaria in all samples and by gender

Variable	Total samples Mean±SD	Females Mean±SD	Males Mean±SD	P-value
Complete blood cell count				
WBC	7.87±2.21	7.83±2.09	8.00±2.55	0.841 [a]
LYM	31.19±13.45	30.86±13.72	32.06±12.80	0.956 [b]
NEU	52.48±18.90	52.69±19.18	51.90±18.34	0.630
BAS	0.41±0.37	0.40±0.37	0.41±0.38	0.953
MON	5.52±2.70	5.33±2.67	6.03±2.78	0.194
HB	12.80±1.45	12.44±1.12	13.85±1.78	<0.001 [a]
HCT	39.68±7.46	38.95±8.05	41.74±5.00	0.065
EOS	2.03±1.74	1.69±1.44	2.90±2.11	0.001
PLT	1580.34±14559.47	292.91±225.89	544265±29115.96	0.185
Thyroid function				
T4	8.58±1.76	8.54±1.83	8.71±1.57	0.549 [a]
TSH	2.65±2.55	2.86±2.81	2.01±1.28	0.059
anti-TGA	74.62±189.7	74.09±145.89	64.82±157.06	0.449
anti-TPO	71.82±148.5	82.41±207.77	47.74±109.24	0.956
Liver enzymes				
SGOT	18.86±10.31	16.92±8.09	24.64±13.72	<0.001
SGPT	47.20±16.37	16.97±8.80	30.87±26.56	<0.001

WBC: White Blood Cell, LYM: Lymphocyte, NEU: Neutrophil, BAS: Basophil, MON: Monocyte, HB: Hemoglobin, HCT: Hematocrit, EOS: Eosinophil, PLT: Placates, T4:Tyroxine, TSH: Thyroid Stimulating Hormone, anti-TGA: Anti-transglutaminase antibody, anti-TPO: anti-thyroid Peroxidase, SGOT: Serum Glutamic-Oxaloacetic Transaminase, SGPT: Serum Glutamic Pyruvic Transaminase.

[a] Independent t-test

[b] Mann-Whitney test

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Discussion

In this study, it was well shown that in order to diagnose patients with chronic urticaria with or without angioedema, specific laboratory tests of autologous serum therapy and assessment of thyroid parameters are necessary. The majority of our subjects were females with an average disease duration of 12.53 years. Therefore, chronic urticaria is higher in female patients (73.33%) who are mainly in the third and fourth decades of their lives compared to men (26.71%) with an average duration of the disease of 4.25 years. This is in line with the study of Ghaffari et al., whose results showed that 71% of patients with chronic urticaria are female (19).

The age range of patients examined in this study was 4 to 66 years, indicating that chronic urticaria affects people in different age groups, but people older than 20 years have a higher risk of developing the disease. In other words, this disease is more common in adults in the age range of 20 to 50 years, and other studies have reported that most of the affected age group is between 30 and 40 years old (20). In addition, in different studies, the average age of patients has been reported to be about 35 years (21), which is approximately equal to the average age of patients in our study. The average duration of chronic urticaria in all our patients was 3.75 years, which is not significantly different from the average duration reported in other studies (21).

All these findings indicate that urticarial lesions at a younger age are more likely to improve compared to older ages and may have a longer duration at older ages. In other words, the high frequency and prevalence of chronic urticaria is directly related to increase in the patient's age, higher healing possibility of skin lesions and more stability of the disease in higher ages (21). In a large number of our patients, the frequency of chronic urticarial lesions with angioedema was 75%, which is much higher than the amount reported in the study of Sussman et al. (41%) (22) and other studies (21, 23).

In addition, a positive association between atopic diseases such as allergic rhinitis, atopic eczema and asthma with a frequency of 59.5% was observed in our results. Similarly, such a positive relationship between the prevalence of atopic diseases (38.6%), especially allergic rhinitis, in patients with chronic urticaria was much higher than other previously reported allergic diseases (24). Another study found that skin allergy testing for airborne allergens was positive in only 12 patients (15%) out of 78 patients with chronic urticaria (25). The reason for this statistical difference in different studies and our study regarding the association between atopic diseases and chronic urticaria can be related to different definitions and different levels of evaluating this variable based on clinical symptoms, skin sensitivity tests or laboratory tests (21). Studies have shown that there is no direct relationship between the severity and duration of chronic urticaria and the association with other atopic diseases (including allergic rhinitis, atopic eczema, and asthma). However, symptomatic treatment of chronic urticaria may be possible with high doses of antiallergic drugs such as the new generation of antihistamines (Bilastine) (26).

Similar to our findings, other studies (27) have reported an increase in vascular markers with eosinophil and neutrophil infiltration, including skin lesions in chronic idiopathic urticaria with normal white blood cells in most patients, showing no significant difference between the genders, which may lead to tissue edema stimulation (27). The association between autoimmune disorders and chronic urticaria has been well established with a positive autologous skin test in about 50% of patients with chronic urticaria (4). Contrary to these reports, the results of autologous skin serum test in the present study showed a high frequency of positive serum skin test (74.28%) and a significant difference in Total Symptom Score (TSS) between the two genders in patients with chronic urticaria.

Examination of the association between chronic urticaria and thyroid disorders (thyroid autoimmunity) in this study showed that the prevalence of positive thyroid antibodies in patients with chronic urticaria compared with the same number of normal people without a specific disease ranged from 14 to 29%. Confirming the findings of Ghaffari et al.'s study, according to which all patients with chronic urticaria had positive thyroid antibody tests (TPA, TGA) (36.6%), our data showed decrease in TSH levels in 3 patients and normal T4 and abnormal increase in levels of anti-thyroglobulin and anti-peroxidase antibodies in 49 patients (23.33%), which indicate mild hypothyroidism and the rest of patients showed no thyroid dysfunction.

Despite the association between thyroid disorders such as hypothyroidism and hyperthyroidism and the etiology of urticaria or chronic angioedema, one of the causes of chronic urticaria in most people with normal thyroid function may be the presence of anti-thyroid antibodies. Thyroid disorders may be

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involved in the pathogenesis of urticarial lesions, rather than through direct autoimmune effects (positive anti-thyroid antibodies) (21). Therefore, according to various reports on chronic urticaria, despite the increase in immunoglobulin E, if no cause for its pathogenesis is found, thyroid tests should be evaluated for thyroid antibodies and if positive, they should be treated (28).

Contrary to previous studies (29, 30), ANA level was negative in 94.76% of our patients and positive in only 5.23% of patients over 16 years of age, indicating that not only are such laboratory tests ineffective, but also impose additional costs on patient. Evaluation of liver panel which includes functional activity of liver enzymes SGOT and SGPT, similar to the study of Coskun et al. (31), indicated abnormal increase in serum levels of these two enzymes separately and simultaneously in a number of patients, especially in men. It could possibly indicate a serious liver complication, namely fatty liver, and an increase in the accumulation of fat in the liver of these people.

One of the limitations of the present study is the lack of patients' clinical information to evaluate clinical symptoms and the absence of a control or normal group to compare with the patient group and also the small sample size because a small sample size can affect the results of the study and make the interpretation of the results be done with caution. By conducting more studies with a larger sample size, better results can be achieved.

According to the results of this study, laboratory tests such as CBC, liver enzymes, ANA and stool tests are not recommended to diagnose most patients with chronic urticaria with or without angioedema. In fact, due to the high frequency of thyroid parameters in serum and the high percentage of positive autologous skin test in patients (especially young and middle-aged women compared to men), autologous serum therapy and thyroid parameters along with history and detailed clinical examination seem essential.

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