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Anxiety and Depression Levels in Patients with Chronic Spontaneous Urticaria and Their Relationship with Disease Activity

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ABSTRACT

Objective: Various etiological factors and mechanisms play a role in the development of chronic spontaneous urticaria (CSU), but no specific cause can be found in most cases. Emotional factors are also implicated in the etiology of chronic urticaria, which is considered among psychocutaneous diseases. We aimed to determine the levels of depression and anxiety in patients with CSU and to investigate whether they are related to disease activity..

Materials and Methods: The Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) were used to assess depression and anxiety symptoms. Urticaria activity score (UAS-7) was used to evaluate the disease activity. The patient and control groups were questioned and recorded in terms of sociodemographic characteristics.

Results: Of the 45 patients included in the study, 75.5% were female, aged between 18 and 61 years with a mean age of 38.3±12.5 years. When the demographic data of the patient and control groups were compared, no significant difference was found, but mean BDI and BAI scores were higher in the patient group. In addition BDI and BAI scores were higher in patients with higher disease activity. A weak positive correlation was found between UAS-7 scores and BDI and BAI scores (p=0.05, r=0.294, p=0.01, r=0.382, respectively). When BDI and BAI scores were compared with demographic data in the patient group, BAI scores were found to be higher in patients with a family history of psychiatric illness, and BDI scores were found to be higher in patients with angioedema.

Conclusion: The chronic nature of the disease may affect the psychological status of the patients. It is still unknown whether the observed psychiatric comorbidities develop as a consequence of chronic urticaria or, on the contrary, constitute a predisposition for chronic urticaria. Therefore, when evaluating patients with chronic urticaria, the psychiatric status should also be assessed.

Keywords: Chronic spontaneous urticaria, depression, anxiety, disease activity

INTRODUCTION

Urticaria is an erythematous, scaly, pruritic disease characterized by papules and plaques of various sizes involving the superficial dermis (1). If it lasts less than 6 weeks, it is called acute urticaria (AU), and if it lasts longer than 6 weeks, it is called chronic urticaria (CU). There are two subtypes of chronic urticaria: chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIU). The prevalence of chronic urticaria in the general population is approximately 1% (0.5-5%) (2). Chronic urticaria affects women twice as often as men and usually begins in the third to fifth decades (3). CU, a self-limiting disease, usually lasts between two and five years, with symptoms persisting for more than five years in 20% of the patients (4). Angioedema may occur in 40% of the patients (5). Various etiological factors and mechanisms play a role in the development of CSU, but in most cases, no specific cause can be found. The pathogenesis of the disease

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is not fully understood. Infections, food intolerance, coagulation cascade, inflammation, and autoimmunity are emphasized in the pathogenesis (6). Emotional factors are also implicated in the etiology of chronic urticaria, which is considered among psychocutaneous diseases (7). It is estimated that at least 30% of patients with skin diseases have significant psychiatric disorders (8). Psychiatric complications have been shown to develop frequently in patients with CU (8-11). The most common psychiatric problems are depression, anxiety, and somatoform disorders (12). These psychiatric disorders also negatively affect the quality of life (7,8). The effect of CU on the quality of life has been reported to be similar to cardiovascular diseases (13). The pathophysiology is not clearly known. Several studies have shown that children and adolescents with chronic illnesses are more likely to develop mental health disorders (14). Hypothalamic-pituitary-adrenal axis (HPA) dysregulation is thought to contribute to the relationship between psychological symptoms, stress, and atopic immune responses (15). The central nervous system regulates immune system functions through the neurotransmitters, neuropeptides, and cytokines it secretes (16). During an allergic or atopic response, inflammatory cytokines can cross the blood-brain barrier and activate neuroimmune mechanisms associated with behavioral and emotional modulation (17,18). It has been thought that dysregulated secretion of proinflammatory cytokines associated with autoimmunity may play an important role in the comorbid relationship between CU and psychiatric disorders (19).

In our study, we aimed to determine the levels of depression and anxiety in patients with chronic spontaneous urticaria and to investigate whether they are related to disease activity.

MATERIAL and METHODS

The study included 45 CSU patients who presented to the Immunology and Allergy clinic between January 2022 and June 2022 and 45 healthy volunteers homogeneous with the patient group in terms of age and gender as the control group. Suspected food and drug use; respiratory, gastrointestinal, skin, and urinary tract infections; exposure to contact allergens, insect bites, autoimmune diseases, malignancies, psychiatric diseases, inflammatory skin diseases, and triggering physical agents that may cause urticaria were evaluated and all these causes excluded in the patient group. Patients with urticaria lasting longer than 6 weeks and whose with no definite eliciting factor were defined as CSU (20). Exclusion criteria were as follows: acute urticaria, diagnosis of psychiatric disease, psychiatric treatment, diagnosis of neurological disease affecting cognitive functions, mental retardation, concomitant malignancy, chronic diseases such as coronary artery disease, diabetes mellitus, corticosteroids, and immunosuppressive treatment. The patient and control groups were questioned and recorded in terms of their education level, employment status, marital status, whether they had children, and family history of psychiatric illness. In addition, the duration of the disease, urticaria treatment, presence of angioedema, and presence of atopic disease were evaluated according to the history of the patient group. Total immunoglobulin (Ig)E, antinuclear antibody (ANA), and antithyroid peroxidase antibody (Anti-TPO) results were recorded by searching the file archive system. All subjects included in the study were informed about the study and verbal and written informed consent was obtained. This prospective study protocol was approved by the local ethics committee (approval number: 2022/127660)

Assessment of Urticaria Disease Activity

UAS-7, which includes the sum of the 7-day urticaria activity score according to the number of wheals and itching severity, was used to evaluate the disease activity. Disease activity was evaluated in four groups as UAS 7 score ≤6: well controlled, 7-15: mild, 16-27: moderate, and 28-42: severe urticaria (21).

Assessment of Anxiety and Depression Levels

The Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) were used to assess depression and anxiety symptoms. The BDI and BAI consist of 21 items (four-point scale) that were self-reported within the last week. (22,23) Total Beck Anxiety Inventory score was evaluated as 0-7: no anxiety, 8-15: mild, 16-25: moderate, and 26-63: severe anxiety. Total Beck Depression Inventory score was evaluated as 0-9: minimal depression, 10-16: mild, 17-29: moderate, and 30-63: severe.

Statistical Analysis

SPSS for Windows version 20.0 software was used for statistical analysis of the data. Quantitative data were expressed as mean ± standard deviation (SD), median [min-max], and qualitative data as number (n) and percentage (%). Normality analysis of the data was performed using

the Kolmogorov-Smirnov test. The Mann-Whitney U test and Student-t test were used according to the normality distribution of the data. For categorical variables, the chi-square test was used to compare two categorical groups. Spearman Correlation was used for the correlation of numerical data according to the distribution analysis. The correlation coefficient (r) was evaluated as 0-0.19: very weak, 0.2-0.39: weak, 0.4-0.59: moderate, 0.6-0.79: high, and 0.8-1.0: very high (24). $p<0.05$ was considered statistically significant.

RESULTS

Of the 45 patients included in the study, 34 (75.5%) were female, aged between 18 and 61 years, with a mean age of 38.3±12.5 years. Of the 45 patients in the control group, 34 (75.5%) were female, aged between 20 and 55 years, with a mean age of 38.6±10.3 years. There was no significant difference between the groups in terms of age and gender distribution (p=0.186, p=1.0). The median disease duration in the patient group was 60 months (2-504 months) and the disease duration was less than 1 year in 22.2%, between 1 and 5 years in 31.1%, and more than 5 years in 46.6% of the patients. According to UAS-7, 15.5% of patients had well-controlled, 22.2% mild, 13.3% moderate, and 48.9% severe disease activity. Angioedema accompanied 40% of the patients and 40.9% had elevated serum total IgE levels (>100 IU/ml). 33.3% had a history of atopic disease. ANA positivity was present in 11.1% of patients and anti-TPO positivity was present in 22.2%. 42.2% of patients were receiving oral antihistamine therapy (OAH) alone, 33.3% were receiving oral antihistamine therapy in combination with omalizumab, and the remaining patients were not receiving any treatment for chronic urticaria (Table I).

Table I: Demographic characteristics and laboratory findings of the patient group and distribution by gender.

	Patients (n=45)	Female (n=34)	Male (n=11)	p-value
Age (mean± SD, years)	38.3±12.5	39.7±13.0	34.2±10.5	0.219
Duration of disease (month)				
Median [min - max]	60 [2-504]	66 [2-504]	36 [24-120]	0.958
UAS-7, n (%)				0.670
Well controlled (≤ 6)	7 (15.5)	7 (20.6)	0	
Mild (7-15)	10 (22.2)	6 (17.6)	4 (36.4)	
Moderate (16-27)	6 (13.3)	4 (11.8)	2 (18.2)	
Severe (≥28)	22 (48.9)	17 (50.0)	5 (45.4)	
Treatment, n (%)				0.648
No	11 (24.4)	9 (26.5)	2 (18.2)	
OAH	19 (42.2)	14 (41.2)	5 (45.4)	
OAH + Omalizumab	15 (33.3)	11 (32.3)	4 (36.4)	
Angioedema, n (%)				0.313
No	27 (60.0)	19 (55.9)	8 (72.7)	
Yes	18 (40.0)	15 (44.1)	3 (27.3)	
History of atopic disease, n (%)				0.203
No	30 (66.7)	21 (61.8)	9 (81.8)	
Yes	15 (33.3)	13 (38.2)	2 (18.2)	
ANA, n (%)				0.083
Negative	40 (88.9)	29 (85.3)	11 (100.0)	
Positive	5 (11.1)	5 (14.7)	0	
Anti-TPO, n (%)				0.196
Negative	35 (77.8)	25 (73.5)	10 (90.9)	
Positive	10 (22.2)	9 (26.5)	1 (9.1)	
Total IgE, n (%)				0.510
Normal	13 (59.1)	10 (71.4)	3 (37.5)	
High (>100 IU/ml)	9 (40.9)	4 (28.6)	5 (62.5)	

SD: Standard deviation, **min:** Minimum, **max:** Maximum, **UAS-7:** 7-day urticaria activity score, **OAH:** Oral antihistamines, **ANA:** Anti-nuclear antibody, **TPO:** Thyroid peroxidase, **Ig:** Immunoglobulin**.**

When the demographic data of the patient and control groups were compared, no significant difference was found, but mean depression scores were significantly higher in the patient group and anxiety scores were higher in the patient group but not significantly (Table II). When the urticaria disease activity score was compared with depression and anxiety scores, BDI and BAI scores were higher in patients with higher disease activity (Table III, Table IV). A weak positive correlation was found between UAS-7 scores and BDI and BAI scores (p=0.05, r=0.294, p=0.01, r=0.382, respectively). When BDI and BAI scores were compared with demographic data in the patient group, BAI scores were found to be significantly higher in patients with a family history of psychiatric illness, and BDI scores were found to be significantly higher in patients with angioedema.

DISCUSSION

CSU is a mast cell-mediated disease of unknown cause characterized by recurrent urticaria and/or angioedema lasting longer than six weeks. The female gender predominates and the mean age of onset is usually between the third and fifth decades (25-29). In our study, female gender predominance was found similar to the literature and the mean age of the patients was 38.3 years. The duration of disease in chronic urticaria varies between two and five

Table II: Comparison of demographic data, anxiety and depression levels of the patient and control groups.

	Patients (n=45)	Control (n=45)	p value
Age (mean± SD, years)	38.3±12.5	38.6±10.3	0.18
Female, n (%)	34 (75.6)	34 (75.6)	1.0
Education, n (%)			
Primary	19 (42.2)	18 (40.0)	0.9
High school	9 (20.0)	8 (17.7)	
University	17 (37.8)	19 (42.2)	
Employment status, n (%)			
Don't work	16 (35.5)	14 (31.1)	0.77
Working at a job	22 (48.9)	24 (53.3)	
Student	7 (15.6)	7 (15.6)	
Having children, n (%)			
No	15 (33.3)	18 (40.0)	0.51
Yes	30 (66.7)	27 (60.0)	
Family history of psychiatric illness, n (%)			
No	36 (80.0)	41 (91.1)	0.13
Yes	9 (20.0)	4 (8.9)	
Marial status, n (%)			
Single	15 (33.3)	13 (28.8)	0.41
Married	25 (55.6)	30 (66.6)	
Widow	5 (11.1)	2 (4.4)	
BAI score (mean±SD)	12.46 ± 10.75	4.89±8.65	0.06
BDI score (mean±SD)	9.53 ± 8.36	3.95 ± 5.33	0.01

SD: Standard deviation, **BAI:** Beck Anxiety Inventory, **BDI:** Beck Depression Inventory

Table III: Comparison of Beck Depression Inventory levels according to the UAS-7 levels.

		Beck Depression Inventory				Total
		Minimal	Mild	Moderate	Severe	
UAS-7	Well controlled	6 (85.7)	1(14.3)	0	0	7
	Mild	9 (90.0)	0	1 (10.0)	0	10
	Moderate	2 (33.3)	1 (16.7)	2 (33.3)	1 (16.7)	6
	Severe	13(59.1)	4 (18.2)	5 (22.7)	0	22
Total		**30(66.7)**	**6 (13.3)**	**8 (17.8)**	**1 (2.2)**	**45**

p=0.05, values are given n (%).

Table IV: Comparison of Beck Anxiety Inventory levels according to the UAS-7 level.

		Beck Anxiety Inventory				Total
		No anxiety	Mild	Moderate	Severe	
UAS-7	Well controlled	5 (71.4)	2 (28.6)	0	0	7
	Mild	6 (60.0)	3 (30.0)	1 (10.0)	0	10
	Moderate	2 (33.3)	1 (16.7)	1 (16.7)	2 (33.3)	6
	Severe	6 (27.2)	6 (27.2)	6 (27.2)	4 (18.4)	22
Total		**19(42.2)**	**12(26.7)**	**8 (17.8)**	**6 (13.3)**	**45**

p=0.01, values are given n (%).

years. In one-fifth of the patients, it lasts longer than five years (4). In our study, the median disease duration was found to be 60 months and 46.62% of the patients had a disease duration of more than 5 years. The reason for this is thought to be that our center is a university hospital.

Emotional factors are frequently emphasized in the etiology of urticaria, which is considered among psychocutaneous diseases (7). There are many studies in the literature investigating the relationship between chronic urticaria and psychological disorders. Although different psychometric methods were used in the studies, the most common psychological disorders found in patients with chronic urticaria were reported to be depression, anxiety, and somatoform disorders (30-32). In a study conducted by Uzunali et al. with 112 patients with chronic urticaria, psychopathology was found in 59 patients. Anxiety was found in 23 patients, depression in 24 patients including major depression in 6 patients, adjustment disorder in 7 patients, somatization disorder in 2 patients, dysthymic disorder in 2 patients, and parasomnia in 1 patient (7). In a study conducted by Hashiro and Okumura. using psychological and physiological tests, a tendency to anxiety, depression, and psychosomatic symptoms was observed in 70% of patients with chronic urticaria, while this rate was found to be 25.6% in the control group (31). Staubach et al. reported that 48% of patients with chronic urticaria had at least one psychiatric disorder. The most common of these was anxiety, followed by depression and somatoform disorder (12). In the study conducted by Topal et al. using the BDI, BAI, and Personality Disorder Test, no significant difference was found in terms of depression and personality disorder, whereas the rate of anxiety was found to be high in the urticaria group. It was reported that there was no significant difference in the frequency of depression and anxiety between male and female urticaria patients (33). In another study using BDI and STAI (State and Trait Anxiety Inventory), no significant difference was found in terms of depression and anxiety (34). In the study conducted by Engin et al., the rate of depression was found to be significantly higher in the evaluation made with the BDI compared to the control group (35). In another study conducted using the BDI and STAI scales in patients with chronic urticaria, depression and anxiety scores were found to be higher in the patient group, and in addition, depression and anxiety scores were found to be higher in women than in men in the patient group (36). In our study, the mean BDI score was found to be significantly higher in the patient group (p= 0.01). Although the mean BAI score was higher in the patient group, no significant difference was found (p=0.06). In the correlation analysis between UAS7 and BDI and BAI scores, a weak positive correlation was found. These findings suggest that urticaria severity is associated with anxiety and depression levels in patients with chronic spontaneous urticaria. This suggests that controlling the disease will have positive effects on anxiety and depression or that controlling depression and anxiety will reduce disease activity. In addition, the BDI score was found to be higher in patients with angioedema. Angioedema negatively affects patients both cosmetically and functionally. It may contribute to depression. When patients with and without a family history of psychiatric disorders were compared, it was found that the BAI score was significantly higher in patients with a family history of psychiatric disorders. This suggests that psychiatric disorders also affect other family members.

The relationship between chronic urticaria and psychosocial status is clearly explained. Prolonged stress can increase mast cell sensitivity by increasing inflammation (37). Stress caused by psychosocial factors may have a direct effect on CSU symptoms via mast cells (38). In addition, considering factors such as the unknown cause of CSU and the duration of the disease, CSU symptoms such as pruritus, swelling, and angioedema may affect sleep, social well-being, and psychosocial status (39,40). In the systemic review by Donelli et al., 18 studies were evaluated. Psychosocial factors have been observed to be correlated with the onset of CSU and worsening of symptoms, and CSU symptoms have been observed to negatively affect psychosocial factors. The most common psychosocial factor associated with CSU onset/worsening of symptoms was stress. It has also been suggested that among CSU populations, certain personality types are more prone to stressful lifestyles or suppressing their emotions so that mental stress can manifest as physical symptoms. In addition mood and anxiety disorders were negatively impacted by CSU symptoms (38).

Chronic spontaneous urticaria is a disease of unknown etiology that negatively affects quality of life. The chronic nature of the disease, recurrence of symptoms despite treatment, sedative effects of antihistamines, and the cosmetic discomfort of the disease may affect the psychological status of the patients. It is still unknown whether the observed psychiatric comorbidities develop as a consequence of chronic urticaria or, on the contrary, constitute

a predisposition for chronic urticaria. Therefore, psychiatric status should be assessed when evaluating patients with chronic urticaria.

Conflict of Interest

The authors have no conflicts of interest to declare.

Authorship Contributions

Concept: **Songul Cildag, Mesut Ogutcu,** Design: **Songul Cildag, Mesut Ogutcu, Taskin Senturk,** Data collection or processing: **Mesut Ogutcu, Gokhan Sargin,** Analysis or Interpretation: **Songul Cildag, Mesut Ogutcu, Gokhan Sargin,** Literature search: **Songul Cildag, Mesut Ogutcu,** Writing: **Songul Cildag, Mesut Ogutcu, Gokhan Sargin,** Approval: **Songul Cildag, Mesut Ogutcu, Gokhan Sargin, Taskin Senturk.**

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