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The effect of stress on the onset of chronic spontaneous urticaria in the elderly

Wpływ stresu na wystąpienie przewlekłej pokrzywki spontanicznej u osób starszych

Nida Öztop[1], Şengül Beyaz[2]

[1]Division of Adult Immunology and Allergic Diseases, İstanbul Başakşehir Çam and Sakura City Hospital, İstanbul, Turkey
[2]Division of Adult Immunology and Allergic Diseases, Ankara City Hospital, Ankara, Turkey

ABSTRACT

Introduction: Chronic spontaneous urticaria (CSU) can occur at every age, however, knowledge of the elderly with CSU is limited.

Aim: To examine the relationship between the onset of CSU and previous stressful life events, disease activity, and perceived general stress in the elderly age group.

Material and methods: A hundred and sixty-four elderly patients with CSU were included. To evaluate urticaria activity, Turkish-validated seven days Urticaria Activity Score (UAS7) was used. Patients were questioned by physicians to respond "yes" or "no" to evaluate having stress, and their opinion on the relationship between a stressful event and onset of urticaria. Severity of stress level was assessed by using 10-point Visual Analogue Scale (VAS). Patients were divided into two groups according to the VAS. VAS ≤ 5 and > 5 were considered as patients with no stress (Group 1, $n = 66$), and patients with stress (Group 2, $n = 98$), respectively.

Results: A hundred patients had at least one stressful life event within three months of the onset of CSU. There was a strong correlation between having stress and onset of CSU ($r = 0.871$, $p < 0.001$), a positive correlation was determined between VAS and UAS7 ($r = 0.418$, $p < 0.001$). Concomitant disease history and UAS7 were significantly higher in Group 2 than in Group 1 ($p = 0.018$ and $p < 0.001$, respectively).

Conclusions: Stressful life events and perceived high stress may be a trigger for CSU in the elderly. To control CSU in the elderly, having stressful life events should be questioned and multidisciplinary management including psychiatry consultation should be done.

KEY WORDS

urticaria, elderly, stress, urticaria activity score, visual analogue scale.

ADDRESS FOR CORRESPONDENCE

Nida Öztop, Division of Adult Immunology and Allergic Diseases, İstanbul Başakşehir Çam and Sakura City Hospital, İstanbul, Turkey, e-mail: nida_oztop@hotmail.com

INTRODUCTION

Chronic urticaria (CU) is a skin lesion which is characterized by wheals, angioedema, or both for at least 6 weeks and classified into 2 groups including "Chronic Spontaneous Urticaria (CSU)" and "Chronic Inducible Urticaria (CIndU)" [1]. CSU has an increasing prevalence in all age groups and can be a result of lower quality of life [1]. Worldwide population demographics are changing due to an increasing population of the elderly and CSU can be determined in elderly patients the same as adults [2]. In a study, it has been reported that the prevalence of CSU among adults was 0.23% in the United States and more of them were over 50 years [3]. With the increasing elderly population, it is thought that the frequency of urticaria may increase in the elderly. Although many studies in the literature evaluate the prevalence and treatment of CSU in adults and children, there are limited data on the prevalence and mechanism of occurring urticaria in the elderly population [4].

It is well known that multiple triggers like stress, inflammation, autoimmunity, and infection can play a role in the CSU etiology [5]. Several times, in the literature, it has been shown that psychological disorders including post-traumatic stress disorders, depression, and anxiety can be seen in patients with CSU as prevalence range from 32% to 34%, most patients with CSU are thought to suffer from general psychological disorders [6–8] and psychological comorbidities are higher among patients with CSU than healthy population [8]. The fact that urticaria is a mast cell (MC)-related disease is confirmed by the demonstration of MC degranulation in the skin lesion of patients with CSU and increased histamine level in the skin lesion, as well as the positive response to antihistamine treatment [9]. It has been suggested that the skin is both a stress sensor and a target organ in which stress reactions occur through interactions between the hypothalamic-pituitary-adrenal axis, proinflammatory cytokines, mast cells, T cells, and inflammatory neurogenic pathways. This hypothesis explains the possible link between psychological stress and urticaria [10].

It has been argued that the lack of awareness and cognitive impairment associated with stress are factors that make the elderly more susceptible to immune-mediated diseases and death due to environmental poverty and lack of stimuli [11].

AIM

As mentioned before, since stress increases MC-related diseases and the increased stress associated with aging in the elderly is known, our aim of this study was to examine whether there was a relationship between the onset of urticaria and previous stressful life events, disease activity, and perceived general stress in the elderly age group.

MATERIAL AND METHODS

PATIENT SELECTION AND STUDY DESIGN

This real-life and cross-sectional study included 164 elderly patients who were attended the adult allergy outpatient clinic with CSU according to the recent urticaria guidelines [1]. Elderly patients were defined as patients aged ≥ 65 years according to the World Health Organization definition [12]. Patients with CSU using or not using antihistamine were included into the study, however, patients who did not obtain to included in the study, having a diagnosed psychiatric disease or using antipsychiatry and sedative drugs, and patients that could not give an anamnesis by themselves were excluded from the study.

Başakşehir Çam and Sakura City Hospital's ethics committee approved this study (Approval Number 2022.06.205) in accordance with the Declaration of Helsinki and written informed consent was obtained from all patients.

CLINICAL DATA COLLECTION

Demographic and clinical characteristics of the patients including body mass index (BMI), sex, age, disease duration, smoke habits, and occupation information were collected from the patients' records. To evaluate the urticaria activity of the patients, Turkish validated seven days Urticaria Activity Score (UAS7) was used [13]. According to UAS7, patients were classified as severe CSU (UAS7 = 28–42), moderate CSU (UAS7 = 16–27), mild CSU (UAS7 = 7–15), and well-controlled CSU (UAS7 = 0–6) [1, 13]. Baseline medication score (MS) was assessed by the physicians; accordingly, the following scores were applied for each drug: antihistamines (regular dose: 2 points; four times the standard dose: 8 points), corticosteroids (prednisone < 11 mg or equivalent: 5 points; prednisone: 11–25 mg or equivalent: 10 points; prednisone > 25 mg or equivalent: 15 points), cyclosporine (3 mg/kg: 8 points) and hydroxychloroquine (6 points) and montelukast (2 points) [14].

EVALUATION OF STRESS

The patients were questioned by the physicians to respond "yes" or "no" to evaluate having stress. And, questions if the patients had stress, about stress-related events including fear of death, economic problems, death or severe illness of a close relative, divorce history, having a newly diagnosed concomitant disease, changing the living area, inability to work after retirement, worsening of concom-

itant diseases, start to live alone or patient care of a close relative were asked by physicians. Also, patients were questioned about their opinion on the relationship between having a stressful event and the onset of urticaria as "yes" or "no". The severity of stress level was assessed by using 10-point Visual Analogue Scale (VAS), which is a Likert scale [15]. On the VAS, patients were asked to score their stress levels from 0 to 10 and a score of zero was considered as no stress, a score of 10 was considered the highest stress score. Patients were divided into two groups according to the VAS, and, VAS ≤ 5 was considered as patients with no stress (Group 1), and VAS > 5 was considered as patients with stress (Group 2) [15].

ETHICS STATEMENT

The study protocol was approved by Başakşehir Çam and Sakura City Hospital Ethics Committee (Approval Number 2022.06.205). The study was conducted in accordance with the principles of the Declaration of Helsinki. All participants were informed about the nature of the study and written informed consent was obtained.

STATISTICAL ANALYSIS

The data were analyzed using the Statistical Package for Social Sciences (SPSS Inc. Armonk, NY, USA) v25.0, and GraphPad Prism Software 8 (San Diego, CA, USA) was used for obtaining the figure. Demographic and clinical features were assessed by descriptive analysis and shown as percentages and mean ± standard deviation or median with interquartile range (IQR) 25–75 according to the data distribution. The Kolmogorov-Smirnov test was conducted to assess the distribution pattern of the quantitative data. Continuous variables were compared by independent *T* test or Mann-Whitney *U* test between two groups according to the data distribution. The categorical variables were compared with the χ^2 test. For the correlation between having stress and urticaria onset, and between VAS and UAS, Spearman and Pearson correlation analysis was used. In all analyses, *p*-values < 0.05 were considered statistically significant.

RESULTS

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE PATIENTS

The mean age of the patients was 69.96 ±4.37 years and more than half of the patients (*n* = 116, 70.7%) were female. While 28% (*n* = 46) of patients had smoking habits, none of them had alcohol habits. Concomitant angioedema history was determined in 42.7% (*n* = 70) of patients, and 130 (79.3%) patients had comorbid diseases including diabetes, hypertension, thyroid disease, cardiovascular diseases, autoimmune diseases, or others. According to UAS7, 51 (31.1%), 23 (14%), and 90 (54.9%) patients had mild, moderate, and severe urticaria, respectively. The demographic and clinical characteristics of the patients were summarized in Table 1.

RESULTS OF HAVING A STRESSFUL LIFE EVENT AND CORRELATION ANALYSIS BETWEEN STRESS AND ONSET OF URTICARIA

One hundred (61%) patients had at least one stressful life event within three months of the onset of urticaria. While the most common stressful event reason was

TABLE 1. Demographic and clinical characteristics of the patients (*n* = 164)

Features	Value
Age [years] mean ± SD	69.96 ±4.37
Gender, *n* (%):	
Female	116 (70.7)
Male	48 (29.3)
BMI [kg/m^2] mean ± SD	26.79 ±0.3
Smokers, *n* (%)	46 (28)
Concomitant angioedema, *n* (%)	70 (42.7)
Working status, *n* (%):	
Never worked in lifetime	81 (49.4)
Retired	83 (50.6)
Comorbid diseases, *n* (%):	130 (79.3)
Diabetes mellitus	52 (39.2)
Hypertension	84 (63.8)
Thyroid diseases	15 (11.5)
Cardiac diseases	23 (17.7)
Malignancy	6 (4.6)
Autoimmune diseases	2 (1.5)
Others	12 (9.2)
Duration of urticaria [years] median (IQR 25–75)	4 (2–8)
UAS7 (mean ± SD)	26.10 ±14.27
MS (median, IQR 25-75)	6 (2-15)
Urticaria severity, *n* (%):	
Mild	51 (31.1)
Moderate	23 (14)
Severe	90 (54.9)

BMI – body mass index, UAS7 – seven days urticaria activity score, MS – medication score, IQR – interquartile range, *n* – patient number.

TABLE 2. Reasons of stressful life events ($n = 100$)

Reasons	Value
Economic problem, *n* (%)	31 (18.9)
Death or severe illness of a close relative, *n* (%)	22 (13.4)
New diagnosed concomitant disease, *n* (%)	6 (3.7)
Fear of death, *n* (%)	8 (4.9)
Changing the living area, *n* (%)	5 (3)
Inability to work after retirement, *n* (%)	9 (5.5)
Patient care of a close relative, *n* (%)	7 (4.3)
Worsening of concomitant disease, *n* (%)	2 (1.2)
Divorce history, *n* (%)	2 (1.2)
Start to live alone, *n* (%)	8 (4.9)

n – patient number.

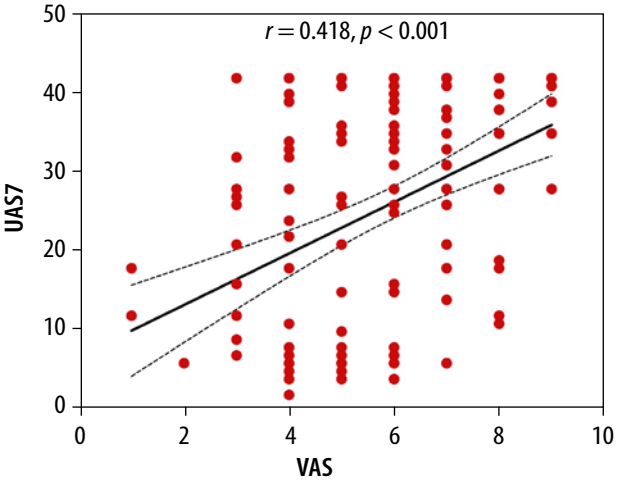

FIGURE 1. Correlation analysis between VAS and UAS7

UAS7 – 7 days urticaria activity score, VAS – visual analogue scale.

the economic problem ($n = 31$, 18.9%), the second most common reason was the death or serious illness of a close relative ($n = 22$, 13.4%). The reasons of the stressful event were summarized in Table 2. The median VAS score of patients was 5.92 ±1.83 points. When the patients were questioned about their opinion on the relationship between having a stressful life event and the onset of urticaria, there was a strong correlation between the two ($r = 0.871$, $p < 0.001$). Additionally, a positive correlation was determined between VAS and UAS7 ($r = 0.418$, $p < 0.001$) (Figure 1).

COMPARISON ANALYSIS OF DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PATIENTS OF TWO GROUPS

While 66 (40.2%) patients were in Group 1, 98 (59.8%) patients were in Group 2. There were no significant differences in gender, age, BMI, and smoking habits between the two groups ($p > 0.05$ for each). Concomitant disease history and UAS7 were significantly higher in Group 2 than in Group 1 ($p = 0.018$ and $p < 0.001$, respectively). Additionally, when we compared the urticaria severity in two groups according to UAS7, mild urticaria was

TABLE 3. Comparison analysis of the demographic and clinical features between two groups

Features	Group 1 ($n = 66$)	Group 2 ($n = 98$)	*P*-value
Age [years] mean ± SD	69.48 ±3.65	70.28 ±4.79	0.227
Gender, *n* (%):			
Female	46 (69.7)	70 (71.4)	0.862
Male	20 (30.3)	28 (28.6)	
BMI [kg/m^2] mean ± SD	26.35 ±0.32	26.97 ±0.29	0.369
Smoking habits, *n* (%)	25 (37.9)	23 (23.5)	0.055
Concomitant disease history, *n* (%)	46 (69.7)	84 (85.7)	**0.018**
Concomitant drug usage for the other diseases, *n* (%)	46 (69.7)	82 (83.7)	**0.028**
Duration of urticaria [years] median (IQR 25–75)	4 (2–9.5)	4 (2–8)	0.559
UAS7 (mean ± SD)	20.33 ±14.06	30 ±13.11	**< 0.001**
MS (median, IQR 25–75)	6 (2–15)	6 (2–15)	0.694
Urticaria severity, *n* (%):			
Mild	31 (47)	20 (20.4)	**< 0.001**
Moderate	12 (18.2)	11 (11.2)	0.253
Severe	23 (34.8)	67 (68.4)	**< 0.001**

BMI – body mass index, IQR – interquartile range, MS – medication score, *n* – patient number, UAS7 – 7 days urticaria activity score.

significantly lower in Group 2 than in Group 1 (n = 20 (20.4%) vs. 31 (47%), $p < 0.001$), whereas severe urticaria was significantly higher in Group 2 than in Group 1 (n = 67 (68.4%) vs. 23 (34.8%), ($p < 0.001$)). The comparison analysis between the two groups was summarized in Table 3.

DISCUSSION

This novel study has demonstrated for the first time that having stress can induce CSU in elderly patients, additionally, urticaria severity can be influenced by higher stress levels in the elderly. Moreover, it has been shown for the first time that CSU may develop more frequently in the elderly who have had a stressful life event such as economic problem or death of relatives, if there is a concomitant disease.

Adult individuals have higher prevalence of CSU than elderly patients, however, due to comorbid diseases and multi-drug usage, unfortunately, elderly patients with CSU have more complexity such as a higher risk of falls, drug interactions, or physiological disorders [16, 17]. To our knowledge, there are limited data about the elderly with CSU to date, therefore, it is difficult to understand the additional underlying mechanism in elderly patients [2, 4, 17]. In a study including 837 patients from Korea, prevalence of CSU was estimated at approximately 4.5% (n = 37), and in another study from the USA, the prevalence of CSU in the elderly was determined at 0.23% [3, 18]. In our study, we included only elderly patients with CSU and also our study included the highest number of elderly patients with CSU in the literature, and with this finding, we may speculate that the frequency of elderly patients with CSU in Turkey may be higher than in the literature. However, this finding should be supported by further multicenter studies.

Chronic psychological stress is considered an important contributor to mental and physiological disorders in people and stress is defined as physiological and behavioral responses to real or perceived stimuli [19]. Psychological stress can induce MC degranulation by stimulating the release of corticotropin-releasing hormone (CRH) into the serum and in case of acute stress, increased serum CRH may stimulate MCs, resulting in an increase in skin vascular permeability. In addition, MCs can also synthesize CRH and express CRH receptor-1 (CRHR-1) [20–23]. The effects of psychological disorders including depression, anxiety, and stress on dermatological diseases and allergic conditions have been studied for a long time and it has been shown several times that physiological stress can induce and cause worsening psoriasis, CU, or cutaneous mastocytosis [6, 8, 10, 24, 25]. Although there is a general decrease in all physiological functions in the elderly, they may have multiple concomitant diseases and this may cause additional psychological stress due to multiple drug use, need for care, and frequent hospital admissions [24, 26]. In our study, we have determined that 98 (59.8%) of 164 patients presented with urticaria, which they thought occurred after a stressful event and this finding suggested that psychological stress may have an effect on the onset of CSU in the elderly. The most common causes of stress were economic problems, and the death or severe illness of a close relative. Additionally, there was a strong correlation between stress and opinion on the onset of CSU in the patients. In line with these findings, we can speculate that stress can be considered as a trigger for the onset of CSU in elderly patients, and to understand the trigger for CSU, we recommend questioning elderly patients with CSU about a stressful event in their life.

In our study, besides determining that stress may be a trigger for the onset of CSU in elderly patients, we found that urticaria was more serious in those with high stress levels. Additionally, concomitant disease history and drug usage were higher in patients with higher stress levels. Perhaps the accompanying illness and excessive drug usage in our patients were also factors that increased their stress, it is well known that chronic diseases can also induce stress, anxiety, and depression. The importance of multiple drug use in the elderly patient is getting increased [27]. According to our findings, it may be thought that urticaria has a more serious course in these patients because CRH, which can elevate under stress, increases more at high stress levels and causes more MC degranulation. In addition, concomitant disease and drug usage may increase stress in elderly patients. For this reason, we can argue that CSU can be easily controlled with rational drug use and stress management in elderly patients with CSU.

As a limitation of our study, we did not have a control healthy group to compare the stressful event effect on the urticaria onset. However, we determined a strong correlation between having stress and opinion about its effect on the onset of urticaria. We believe that our findings should be supported by multicenter studies involving more patients. Another limitation of our study was that we could not include the laboratory findings of the patients to compare two groups. However, our aim in this study was to evaluate the stress impact on the onset and course of CSU in elderly patients. Therefore, we could not include the laboratory findings of the study group.

CONCLUSIONS

In this study, we have shown that a stressful life event and perceived high stress can be a trigger for the CSU in el-

derly patients and concomitant disease and drug usage may increase the stress level in elderly patients. To control CSU in elderly patients, having stressful life events should be questioned and multidisciplinary management including psychiatry consultation and geriatric consultation should be done for the elderly with CSU.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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