

# Research Paper

## Chronic Urticaria: Seeking the Causes in Iranian Population



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## ABSTRACT

**Background:** Chronic urticaria (CU) is the recurrence of erythematous itching papular skin lesions for at least 6 weeks. Although it is often considered a benign condition, there are reports of the association of chronic idiopathic urticaria with infections, thyroid disease, foods, medications, autoimmunity, neoplasms, and low serum level of vitamin D. We aimed to identify the effect of lifestyle characteristics, environmental factors, family history, and specific comorbidities as potential external eliciting factors on the onset of chronic urticaria.

**Materials and Methods:** The present research was conducted on 141 adult patients diagnosed by CU at the allergy clinics of Azad University hospitals in Tehran from January 2021 to January 2022. A questionnaire on different life events during the past 3 months before the onset of urticaria was developed to evaluate the characteristics of the patients with chronic urticaria. Meanwhile, 58 healthy individuals who were similar to the patients in terms of age range and gender were asked to participate in the study as the control group.

**Results:** The mean age of the patients and the controls were 41.7 years and 39.8 years, respectively. The female and male patients were 105(74.47%) and 36(25.53%), respectively. Only two of the evaluated predisposing factors were meaningful including the use of new medications (23.4% versus 19%;  $P=0.006$ ) and the co-existence of anxiety and depression (14.1% versus 4%;  $P=0.036$ ).

**Conclusion:** Among the different factors evaluated in this study, only two were found to be significant in relationship with CU which are anxiety/depression and medications.

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## 1. Introduction

**C**hronic urticaria (CU) is the recurrence of erythematous itching papular skin lesions for at least 6 weeks with a significant negative impact on the quality of life [1]. CU is classified into two types including spontaneous and inducible, with the former featuring no specific eliciting factor, while the latter has a specific eliciting factor [2]. Lesions arising from the degranulation of cutaneous mast cells lead to the release of histamine as well as cysteinyl leukotrienes, prostaglandins, platelet-activating factors, proinflammatory cytokines, and vasoactive factors [3]. Although it is often considered a benign condition without a known trigger, there are reports of association of chronic idiopathic urticaria with infections, thyroid disease, foods, medications, autoimmunity, neoplasms, and low serum level of vitamin D [3, 4]. Circulating IgG and IgE autoantibodies against soluble and tissue antigens are thought to play an important role in the pathogenesis of autoimmune or autoallergic CU [5].

The purpose of the current study was to assess the impact of lifestyle characteristics, environmental factors, family history as well as specific comorbidities as potential external eliciting factors on the onset of chronic urticaria.

## 2. Materials and Methods

### Study design

The present research was a case-control study on the patients diagnosed with CU at the allergy clinics of Azad University hospitals in Tehran from January 2021 to January 2022. According to the international EAACI/GA2LEN/EuroGuiDerm/APAAACI guideline, CU was defined as those adult patients with recurrent wheals persisting for more than 6 weeks [6]. The exclusion criteria were as follows: The patients being younger than 18 years old, suffering from systemic illnesses, or unwilling to participate in the study. A questionnaire on different life events during the past 3 months before the onset of urticaria was developed to evaluate the lifestyle characteristics of the patients with chronic urticaria. All patients with CU were asked to fill out the questionnaire. Therefore, the data were collected from the interview and the questionnaire. The obtained data were compared with a healthy control group.

### Study population

A total of 141 adult patients with CU referred to allergy clinics of Azad University hospitals were examined as the

case group. Meanwhile, 58 healthy individuals with the same mean age were selected as the control group. After confirming the diagnosis of CU by an allergist, all the participants were interviewed and their demographic information was obtained and recorded. In addition, some predisposing factors including the family history of chronic urticaria, smoking, thyroid disease, anxiety, depression, asthma, allergic rhinitis, severe stressful conditions, traveling abroad, infection, new job, sudden weight gain or loss, moving to a new place, strenuous physical activity, new medications, new foods, alcohol consumption, chronic disorders, and pregnancy were recorded as well.

### Statistical analysis

Data analysis was performed using SPSS software, version 24 (IBM Corp. Released 2016. IBM SPSS Statistics for Windows). The chi-square and Fisher's exact tests were used to compare the categorical variables. The statistical level of  $P < 0.05$  was considered significant.

## 3. Results

The mean age of the patients was 41.7 years and the mean age of the onset of the condition in the patients was 35.83 years. The female and male patients were 105 (74.47%) and 36 (25.53%), respectively.

As shown the [Table 1](#), there was no significant relationship between CU and family history ( $P=0.08$ ), smoking ( $P=0.36$ ), thyroid disease ( $P=0.23$ ), asthma flares ( $P=0.49$ ), allergic rhinitis ( $P=0.34$ ), severe stressful condition ( $P=0.39$ ), traveling ( $P=0.89$ ), infections ( $P=0.39$ ), new jobs ( $P=0.32$ ), weight changes ( $P=0.33$ ), moving to new places ( $P=0.28$ ), and strenuous physical activities ( $P=0.79$ ). The two parameters having a meaningful relationship with CU were the association of anxiety/depression ( $P=0.036$ ) and recent consumption of new medications ( $P=0.006$ ).

## 4. Discussion

CU is one of the most common skin diseases [4] and a common reason for referral to allergy clinics causing considerable trouble for many patients. In the present study, we tried to look into the relationship between CU and the aforementioned lifestyle characteristics. We evaluated several personal behavioral traits, events, and maladies in the last three months before the onset of urticaria, of which only two were significantly related to the development of chronic urticaria including the existence of anxiety/depression as well as new consumption of certain medications capable of inducing urticarial lesions.

**Table 1.** The statistical comparison of the personal behavior, events, and comorbidities in both case and control groups during the last three months before the onset of chronic urticaria

Probable Predisposing Factors	No. (%)		P
	Patients	Healthy Individuals	
Family history of CU	64(45.4)	3(5.2)	0.08
Smoking history	22(15.6)	8(13.8)	0.36
Thyroid disease	35(24.8)	5(8.6)	0.23
Anxiety/depression	20(14.1)	3(4)	0.036
Asthma flare	20(14.2)	4(6.9)	0.49
Allergic rhinitis	40(28.4)	15(25.9)	0.34
Stressful condition	6(47.5)	22(37.9)	0.39
Traveling abroad	13(9.2)	2(3.4)	0.89
Recent infection	19(13.5)	11(19)	0.39
New job	3(2.1)	7(12.1)	0.32
Weight changes	13(9.2)	29(50)	0.33
Moving to a new place	11(7.8)	3(5.2)	0.28
New medication	33(23.4)	11(19)	0.006
Strenuous physical activity	9(6.4)	21(36.2)	0.09
New foods	15(10.6)	10(17.2)	0.55
Alcohol consumption	12(8.5)	7(12.1)	0.51
Chronic disease	66(46.8)	4(6.9)	0.25

IMMUNOREGULATION

CU is classified as a psychodermatological disorder [7]. There is a reciprocal relationship between depression/anxiety and chronic urticaria, where each of these can worsen the other [8]. This means that stress/depression can play a major role in the onset and exacerbation of CU and the other way round [7]. In the present study, we found similar results and demonstrated that depression and anxiety were more common in patients with CU than in healthy control participants. A vicious cycle may occur after the development of these eruptions with scratching playing a role not only in aggravating the condition but also in inducing persistent awareness of the problem without the ability to stop focusing on it, leading to sleep disturbance as well as the aggravation of the anxiety and depression.

The results of this study imply the risk of CU with the use of certain medicines. The use of medications is one of the only two risk factors turning out to be significant

in the present study. One explanation is the co-existence of infection and drug use, which may increase the risk of drug adverse effects over the long run.

A recent cross-sectional analysis estimated that CU affects women twice as many as men [9]. Our findings were in line with these results indicating a higher occurrence of CU in women. Hormonal changes [9] in conditions such as endocrinopathies, menstrual cycle, pregnancy, menopause, and hormonal contraceptives or hormone replacement therapy may lead to sex-dependent immunological impacts, which are responsible for this predilection as suggested by other experts [10].

The existence of a genetic background for CU is supported by the fact that this condition is much more frequent among first-degree relatives of affected individuals [11], yet we did not find such a relationship in our patients. Although we believe that genetic factors play

an important role in disease development and progression, such a relationship is mostly expected in certain subtypes of CU [12], which were not considered in the present study.

In previous studies, smoking was suggested as an important factor in the pathogenesis of CU, probably because it contains chemicals with the potential to worsen the condition [13-15]. It appears that tobacco contact and smoke are associated with skin conditions, and also tobacco contact irritation is more frequent than allergy [16], yet no relationship between tobacco smoke and CU was found in the present study. It has also been found that air pollution, on a greater scale, does not seem to affect the incidence of CU either [2]. Furthermore, moving to a new house or house renovation is suggested as the source of indoor pollutant or allergen exposure and therefore a presumed underlying cause of CU [4]. However, we could not establish such a cause-and-effect relationship in the present study.

Moreover, the association between CU and autoimmune thyroid disease has been a subject of debate in many studies. In a study evaluating the anti-TPO antibody in patients with chronic urticaria, a high prevalence of CU and anti-TPO antibody was detected [17]. It can be assumed that such autoantibodies binding to the surface of mast cells and basophils may increase their sensitivity to specific circulating antigens [18]. Thyroid autoimmunity is tracked in 4.3-54.7% of the patients with CU, yet there is still a lack of studies to support this hypothesis [19]. We could not find such a relationship in our patients, which could be attributed to our sole reliance on the patients' histories lacking lab data at the time of their self-report. In addition, patients with chronic autoimmune conditions usually take multiple medications to control the underlying inflammation of their disorder, and skin lesions may therefore subside in the shadow of immunosuppressive drug consumption.

Although CU and allergic rhinitis may demonstrate seasonal correlations [20], we were unable to find such a link between allergic rhinitis and chronic urticaria. Likewise, no relation was found between asthma and CU in our study unlike previous reports [21]. Similar to our study, the results of a recent study on asthma and CU were in line with our findings [22] as in that study the patients with CU did not show an increased incidence of asthma.

Although food is frequently reported as an eliciting factor of chronic urticaria, such a reaction to food is mostly of pseudoallergenic nature and is not usually regarded as

the source of CU [2] as the results of our study confirm the same. Therefore, we recommend neither a skin prick test to find the relation between food and CU nor strict diets to manage this disease.

It has been suggested that there is a significant association between CU with greater affected body surface and heavier weight and higher BMI [23]. Therefore, it seems likely that visceral fat reduction significantly improves inflammation and reduces immune markers [24], yet we could not find such a relationship in this study.

Alcohol consumption has been reported as the cause of CU in a recently published document in Italy [25]. In our study, we defined alcohol consumption as the level that never reached the point of drunkenness. The results showed that alcohol was not a causative agent of CU in the patients.

Cholinergic urticaria may be the cause of exercise-induced urticaria in some patients, although it may also occur in individuals with chronic spontaneous urticaria. These two kinds of urticaria can be distinguished by their size as the lesions in exercise-induced urticaria are larger with diameters ranging from 10 to 15 mm, while cholinergic urticaria is typically small from 1 to 3 mm [26]. Since cholinergic urticaria may be induced by exercise, it should be distinguished from CU by the fore-mentioned characteristics. The relationship between urticaria and exercise was not meaningful in our study.

One limitation of this research was the small sample size of the study. There was also sole reliance on the patients' memory to collect their allergic histories.

## 5. Conclusion

Among the different factors evaluated in this study, only two were found to be significant including anxiety/depression and new medications. To confirm the role of these parameters in inducing chronic urticaria, further studies are needed to be conducted in the future. Similar to previous studies, other parameters were not significant in causing chronic hives. Therefore, healthcare providers may have difficulty answering the patients' questions about the causes of chronic urticaria. Symptomatic management remains the mainstay of the treatment to improve the quality of life.

## Ethical Considerations

### Compliance with ethical guidelines

This study was carried out following the recommendations of the “Ethics Committee of [Tehran Medical Sciences Branch, Islamic Azad University](#)”. All parents provided written informed consent. The study protocol was approved by the “Ethics Committee of [Islamic Tehran Medical Sciences Branch, Islamic Azad University](#)” (No: IR.IAU.TMU.REC.1400.156).

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### Authors' contributions

Conceptualization: Sepideh Darougar and Mehdi Azarafraz; Methodology: Mehdi Azarafraz, Sepideh Darougar and Seyed Karen Hashemitari; Supervision: Sepideh Darougar and Masoumeh Hemmatyar; Formal analysis: Mehdi Azarafraz; Writing original draft: Seyed Karen Hashemitari; Data curation and writing, review and editing: All authors

### Conflicts of interest

The authors declared no conflict of interest.

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