

## CHRONIC URTICARIA AND STRESS

L. V. Besh<sup>\*1,2</sup>, O. M. Besh<sup>1,2</sup>, O. O. Sorokopud<sup>1,2</sup>, M. O. Kondratiuk<sup>1,2</sup>, O.R. Slaba<sup>1,2</sup>, V. V. Zenin<sup>1</sup>

<sup>1</sup>Danylo Halytsky Lviv National Medical University, Lviv, Ukraine

<sup>2</sup>Medical centre "Dovholittia", Lviv, Ukraine

A – research concept and design; B – data collection; C – data analysis and interpretation; D – writing of article; E – editing of article; F – final approval of article

**Abstract. Introduction.** Skin is the largest human organ. Its main functions are protective, excretory, receptory, thermoregulatory, respiratory, etc. Any metabolic disorders in our body, infectious and autoimmune diseases, toxic lesions, chronic renal diseases and those of gastrointestinal tract, diseases of the blood, liver, gall bladder can manifest as skin lesions, for example, in the form of chronic urticaria (CU). Nervous system also plays a significant role in the development of urticaria.

**Objectives.** Studying the prevalence of urticaria in adult patients, main causes of increased skin itching and rash, effect of stress on the frequency and severity of urticaria exacerbations and treatment effectiveness.

**Materials and methods.** The article presents the results of instrumental and laboratory methods of examination of urticaria patients, as well as comparison of the treatment effectiveness depending on the obtained research findings and stress test results. The study included 75 patients aged 18 and over. Patients in both groups underwent laboratory and instrumental examinations, stress testing (The Kessler Psychological Distress Scale (K10)), and the UAS7-test for urticaria control. The main study included 63 patients with urticaria, who were divided into three groups (depending on the results of the stress test).

**Conclusions.** Nowadays CU is an important global problem. Due to constant itching, sleep disturbances, decrease in performance, cosmetic discomfort, the patients' quality of life is getting worse. Timely diagnosis and prescription of treatment improves patients' well-being and social adaptation.

The research shows that stress exacerbates the course of CU. Patients with high and medium level of stress noticed expressed reduction in rash and itching when treatment included sedative medications.

**Key words:** chronic urticaria, causes, quality of life.

**Introduction.** Chronic spontaneous urticaria is not a single disease, there are a large number of diseases that manifest as urticaria (allergies, infections, parasitoses, endocrine, autoimmune and gastroenterological pathology, neoplasms, etc.).

Urticaria is a multietiological (dermatosis), which clinically manifests in erythematose rash appearing on the skin surface.

Approximately 25 % of global population at least once faced urticaria episodes. Average treatment duration of such patients lasts from one to five years (from first symptoms to establishing the cause and symptoms disappearance). About 14 % of patients are treated longer than 5 years [7]. Urticaria is an important cosmetic issue that affects patients' quality of life [9].

Although chronic urticaria (CU) has classic clinical signs, sometimes its cause may be a mystery a doctor has to solve. Mainly it is stipulated by plural causes and various pathogenic mechanisms. Among urticaria provoking factors are the following: household, pollen and food allergens, physical factors (sun, cold, pressure, vibration), medicine, infectious diseases of CU, hormonal disturbances,

fermentopathies and intestinal diseases. An important potential triggering factor that may intensify clinical symptoms of allergic diseases and also cause skin itching itself and urticaria is stress.

About 80 % of the population of Ukraine feels increased stress due to a full-scale war, constant worries about their own safety and that of their relatives, loss of work or property, separation from relatives and uncertainty about the future. Stress negatively affects the human body and causes exacerbation of all chronic diseases. Allergic diseases, including urticaria, are no exception.

**Overview.** Atopic urticaria is caused due to the influence of endogenic or exogenic factor on the patient's body. Initial contact with an allergen causes sensibilization, while a repeated one results in allergic reaction. Presence of immunoglobulin E (IgE) provokes mastocytes degranulation and release of mediators (histamine, serotonin, bradykinin, etc). An allergen causing skin lesion can be any chemical substance, food products, animal fur, insect bites and other substances. To confirm this diagnosis we do skin allergic samples, detect general and specific antibodies.

The main cause of chronic autoimmune urticaria is increased formation of antibodies (mainly immunoglobulines G (IgG)) to FcRI receptors, less frequently to IgE. They activate basophiles and mastocytes, causing histamine,

serotonin and other mediators release. Also important is the activation of complement system and formation of C5a, which is neutrophils and eosinophils chemoactivator [3]. To this type of urticaria may belong urticaria vasculites, physical urticaria, also it appears in thyroid autoimmune diseases.

Physical urticaria is caused under the influence of pressure, heat, cold and other mechanical stimuli on the patient's skin. Dermatographic urticaria appears after mechanical skin irritation — belt pressure, clothes, pressing actions on the skin. In this form of urticaria rash is often preceded by itching. Rash manifests in the form of line blisters, which appear in the process of itching. Urticaria dermatographism without itching can be observed as a short-term phenomenon with blisters disappearing within 30 minutes. It is present in 3–5 % of the population and does not require treatment. Vibration urticaria is caused by the influence of vibrating objects or parts of objects. Such urticaria symptoms in children can be a diagnostic sign of hereditary vibration angioneurotic edema. Heat contact urticaria appears when there is local heat impact on the skin. Cold urticaria is characterized by blisters appearing after local cold impact. Skin areas, directly affected by cold, do not suffer lesions. Rash is visible around the contact place. Some patients respond to cold with neuromediators release, whereas others with anaphilotoxin synthesis through the complement system. Taking into account development mechanisms, some authors classify cold urticaria variant not as physical urticaria but as a spontaneous one [4].

Chronic infectious diseases are one more cause of skin lesion in the form of urticaria [1]. Nowadays virus hepatitis plays a particular role in urticaria appearance. In 15–20 % of patients, the first clinical manifestations of hepatitis may not be sclera or skin jaundice, but also skin or mucous membranes rashes in the form of urticaria, dryness and skin itching [6]. These symptoms are often combined with myalgias, arthralgias, paresthesias, and other extrahepatic symptoms [7]. The risk group includes patients after blood transfusions, minor or major surgical interventions, tattoos, dental interventions, unprotected sexual acts with an infected person, injection drug addicts. Such patients seek help from allergists or dermatologists

There is evidence that *Helicobacter pylori* infection is associated with [4]. In recent years, there have been studies that showed the connection of this infection with clinical manifestations and explained the pathogenetic mechanism of CU development. *Helicobacter pylori* infection is widespread throughout the world. In addition to the clinical manifestations of gastritis or peptic ulcer disease (epigastrium pain, indigestion, flatulence, heartburn, nausea, etc.), the first and often the only sign of *Helicobacter pylori* infection is urticaria rash on the skin of the face, palms and other parts of the body, skin itching. After unsuccessful attempts to treat rashes on their own, patients turn to allergists or dermatologists.

Helminthes infections are one more cause of chronic urticaria in both children and adult patients [1; 9]. During their life helminthes secrete all metabolic products into the lumen of the host's intestinal (human, animal). Penetrating into the blood, these substances can cause urticaria. Another mechanism of urticaria is the synthesis of IgE group antibodies, which leads to the release of biologically active substances from eosinophils, mast cells and other cells that increase the blood vessels permeability, which in its turn leads to the development of urticaria [9].

The early manifestations of some autoimmune diseases (scleroderma, dermatomyositis, vasculitis, etc.) can be rashes that are very similar to urticaria, and for a long time such patients receive symptomatic treatment without sufficient or long-term clinical effect [3]. Collection of family anamnesis and additional examinations (skin biopsy, laboratory determination of markers of systemic diseases) will help establish a timely diagnosis and treat the underlying cause of the disease.

Another important factor that worsens the course of all diseases, including urticaria, is stress [2; 11]. The skin actively reacts to stress with the involvement of skin immune cells, hormones, and neurotransmitters. Skin immune cells actively regulate tissue inflammation, having pro-inflammatory and anti-inflammatory effects. The mechanism of skin damage under the influence of stress is insufficiently studied. However, nowadays it is known that stress promotes release of large concentrations of corticotrophin-releasing hormone (CRH) in the hypothalamus, which in turn leads to the secretion of adrenocorticotrophic hormone (ACTH) and cortisone, corticosterone by activating melanocortin receptors (MCR). Being activated, keratinocytes produce such cytokines as granulocyte-macrophage colony-stimulating factor, interleukin (IL)-1 $\alpha$ , IL-6 and interferon- $\gamma$  (IFN- $\gamma$ ) and increase the migratory activity of Langerhans cells [2; 11; 13]. Later these substances cause skin inflammation, redness and itching.

**Materials and methods.** Our study included 75 patients over the age of 18 (average age  $(36.29 \pm 1.64)$  years), who consulted an allergist with complaints of spot-vesicular rashes, skin itching, angioedema. 7 patients (5 women and 2 men) only complained of very intense skin itching and redness after scratching. All patients gave consent to participate in the survey and use of personal data in the study.

The patients were divided into two main groups: with manifestations of acute (up to 6 weeks) and chronic (more than 6 weeks) urticaria. The first group included 18 patients (24 %), the second group — 52 patients (76 %). The majority of patients were women (62.6 %). Patients of both groups underwent laboratory and instrumental examination, testing to determine the level of stress, urticaria control test UAS7-test. The main study included 63 patients. They were divided into three groups (1, 2 and 3) according to the

results of the stress test. Each group was divided into two subgroups: A — taking sedatives, B — not taking sedatives. In the defined groups and subgroups, the rate of symptom reduction during the first seven days of treatment was determined by the urticaria control test.

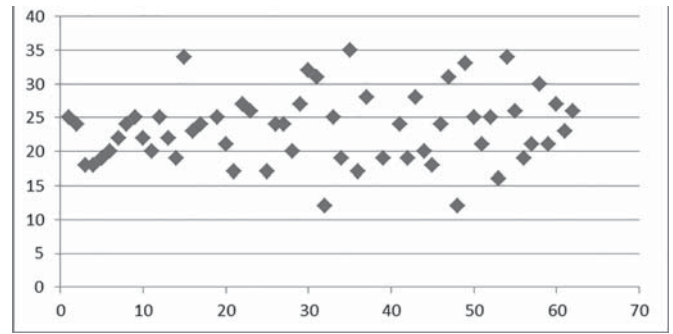
**Results.** After evaluating the results of both groups' examination, it was found that in some of the patients (12 people; 16 %), skin rashes and skin itching were not related to allergies, but were caused by other chronic diseases. In two patients viral hepatitis was detected with increased levels of markers of viral hepatitis and transaminases in the blood. One patient was diagnosed with a thyroid tumor. Three patients with suspected contact allergy underwent patch testing and were diagnosed with hypersensitivity to metals (titanium and nickel) and dyes. Two patients were diagnosed with gluten intolerance by means of laboratory tests and a provocation test. In 4 patients the cause of skin rashes and itching has not been identified.

Table 1 shows the results of the examination of a group of patients who had sensitization to allergens.

**Stress level identification.** At the first visit, the patients were asked to take a test to determine the degree of stress impact on their lives. To do this we used the Perceived Stress Scale (PSS) [7]. The test has 10 questions. The patient evaluates his/her answers on a four-point scale, where 0 — never, 1 — almost never, 2 — sometimes, 3 — quite often, 4 — very often. The test questions are divided into two groups. The first group includes six questions and measures the feeling of lack of control over circumstances (perceived helplessness). The second group includes four questions measuring perceived inability to cope with problems. After counting, the number of points from 0 to 13 is considered to

**Table 1. Results of the examination of a group of patients in whom sensitization to allergens was detected**

Indicator	Clinical manifestations and sensitisation	Number of patients	% from general number of patients
Number of urticaria patients		63	100
Men		20	31.7
Women		43	68.3
Allergic co-morbidities	Allergic rhinitis Allergic conjunctivitis Bronchial asthma Food allergy	27 6 11 7	
Sensibilization to	Pollen allergens Herbs Trees Household allergens Dust mites Cat Dog Fungi Food allergens	12 17 21 3 2 2 5	
The level of total IgE	Min — 84 MO Max — 2347 MO Average value 495 MO		
Eosinophil cationic protein	Min — 16.7 Max — 84.5 Average value — 39.4		



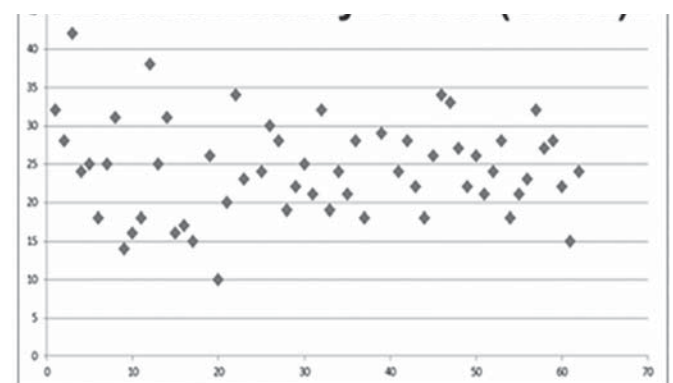
**Fig. 1. Level of Stress in patients with urticaria.**

be a low risk of stress, from 14 to 26 — a moderate level, from 27 to 40 — a feeling of strong stress. According to the obtained results, the patients were divided into three groups: the 1st group with a test score from 0 to 13 points, the 2nd group from 14 to 26, the 3rd group — from 27 to 40 points (Fig. 1).

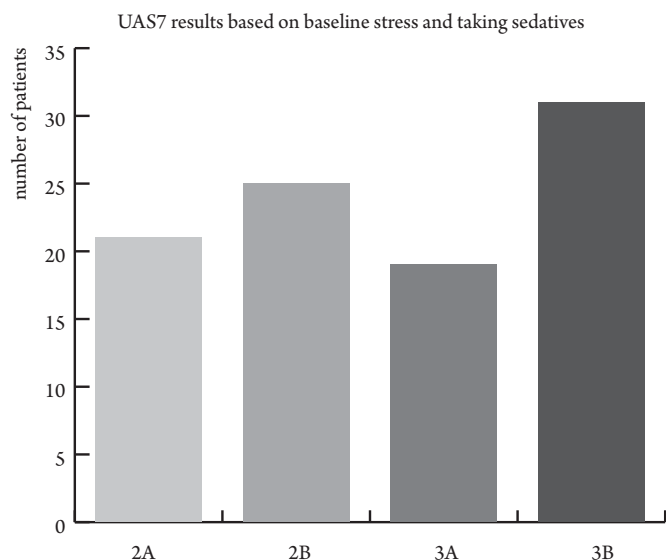
The second and third groups were divided into two more subgroups: 2A (16 people) and 3A (11 people) — took sedative drugs, 2B (28 people) and 3B (3 people) — took only basic drugs to reduce urticaria symptoms and concomitant diseases (antihistamines of the second generation, intranasal glucocorticoids, antagonists of leukotriene receptors, inhaled glucocorticoids and bronchodilators). Correction of treatment was carried out after seven days.

**Control of urticaria symptoms reduction.** In order to monitor the effectiveness of the prescribed treatment, we recommended that patients complete the urticaria activity test (Urticaria Activity Score (UAS7)) [12] at home. During 7 days the patients evaluate the level of rash and skin itching intensity in points from 0 to 3 (where 0 means no symptoms, 3 — the symptoms are very severe) (Fig. 2).

After receiving the results of UAS7 at the second visit, we compared the effectiveness of treatment in all the groups (Fig. 3). In patients of group 2A (moderate level of stress, they took sedatives), the average value was equal to  $(22.4 \pm 1.6)$  points, in patients of group 2B (those who did not take sedatives) —  $(25.1 \pm 1.2)$  points. In the group that was assigned to group 3A at the first visit, this indicator was  $(21.5$



**Fig. 2. Control of urticaria symptoms reduction.**



**Fig. 3. UAS7 test results in patients with urticaria after 7 days of treatment.**

$\pm 1.0$ ) points, in group 3B — ( $30.6 \pm 2.0$ ). Therefore, in patients who entered group 2, there was no significant difference in reduced urticaria symptoms depending on the use of sedative drugs. However, in group 3A patients the reduction in urticaria symptoms was more significant than in group 2A.

**Conclusions.** 1. CU is an important medical and social problem due to the fact that it negatively affects the patient's well-being and reduces quality of life. Unfortunately, nowadays not all the patients can be diagnosed with the final cause of skin rashes and prescribed treatment for long-term or complete remission. But in most patients with urticaria manifestations, the detailed examination and check-up allow to determine the cause of the disease and manage it.

2. Administration of sedative drugs to reduce urticaria symptoms is appropriate in patients with high and moderate levels of stress according to the PSS.

## ХРОНІЧНА КРОПИВ'ЯНКА І СТРЕС

Л. В. Беш<sup>\*1,2</sup>, О. М. Беш<sup>1,2</sup>, О. О. Сорокопуд<sup>1,2</sup>, М. О. Кондратюк<sup>1,2</sup>, О. Р. Слаба<sup>1,2</sup>, В. В. Зенін<sup>1</sup>

<sup>1</sup>Львівський національний медичний університет імені Данила Галицького, Львів, Україна

<sup>2</sup>Медичний центр «Довголіття», Львів, Україна

**Резюме. Вступ.** Шкіра — найбільший орган людини. Основними її функціями є захисна, видільна, рецепторна, терморегуляційна, дихальна. Будь-які порушення обміну в нашому організмі, інфекційні та аутоімунні хвороби, токсичні ураження, хронічні хвороби нирок та шлунково-кишкового тракту, хвороби крові, печінки, жовчного міхура можуть проявлятися ураженням шкіри у вигляді, наприклад, хронічної кропив'янки. Нервова система також відіграє не останню роль у виникненні кропив'янки.

**Мета.** Вивчення поширеності кропив'янки у дорослих пацієнтів, основних причин посилення свербіжів шкіри та висипань, впливу стресу на частоту та тяжкість загострення кропив'янки, ефективність лікування.

**Матеріали та методи.** В статті представлені результати інструментальних та лабораторних методів обстеження пацієнтів з хронічною кропив'янкою, а також порівняння ефективності їх лікування залежно від отриманих результатів досліджень та тесту на стрес. У дослідження увійшло 75 пацієнтів віком від 18 років. Пацієнти обох груп пройшли лабораторне та інструментальне обстеження, тестування на визначення рівня стресу (за шкалою The Kessler Psychological Distress Scale (K10)), тест контролю кропив'янки UAS7-test. В основне дослідження увійшло 63 пацієнти з кропив'янкою, які були розділені на три групи в залежності від результатів тесту на рівень стресу.

**Результати.** У дослідженні показано, що стрес погіршує перебіг хронічної кропив'янки. Пацієнти із середнім та високим рівнем стресу відзначали зменшення висипань та свербіжів шкіри у разі додавання до класичної терапії седативних препаратів.

**Висновки.** Хронічна кропив'янка на сьогодні є важливою проблемою у всьому світі. Через постійний свербіж, порушення сну, зниження працездатності, косметологічний дискомфорт якість життя таких пацієнтів знижується. Вчасна діагностика та призначення лікування забезпечує покращення самопочуття пацієнтів та їх соціальну адаптацію.

**Ключові слова:** хронічна кропив'янка, причини, якість життя, стрес.

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#### Відомості про авторів

##### Л. В. Беш\*

Львівський національний медичний університет імені Данила Галицького;  
Кафедра педіатрії № 2  
доктор медичних наук, професор  
lesya.besh@gmail.com  
ORCID ID: <https://orcid.org/0000-0003-1897-7461>

##### О. М. Беш

Львівський національний медичний університет імені Данила Галицького;  
Кафедра внутрішньої медицини № 2  
к. мед. н, асистент кафедри  
79016 Україна, м. Львів, вул. Пекарська, 576  
besh.olesay@gmail.com  
телефон: +380505496734  
ORCID ID: <https://orcid.org/0000-0003-3349-1291>

##### О. О. Сорокопуд

Львівський національний медичний університет імені Данила Галицького;  
Кафедра внутрішньої медицини № 2  
к. мед. н, доцент кафедри  
79016 Україна, м. Львів, вул. Пекарська, 576  
osorokopud@gmail.com  
ORCID ID: <https://orcid.org/0000-0002-3974-0087>

##### М. О. Кондратюк

Львівський національний медичний університет імені Данила Галицького;  
Кафедра внутрішньої медицини № 2  
к. мед. н, доцент кафедри  
79016 Україна, м. Львів, вул. Пекарська, 576  
marta\_kondratjuk@ukr.net  
ORCID ID: <https://orcid.org/0000-0001-6707-4029>

##### О. Р. Слаба

Львівський національний медичний університет імені Данила Галицького;  
Кафедра внутрішньої медицини № 2  
к. мед. н, асистент кафедри  
79016 Україна, м. Львів, вул. Пекарська, 576  
oksanaslaba24@gmail.com  
ORCID ID: <https://orcid.org/0000-0002-4560-5156>

##### В. В. Зенін

Львівський національний медичний університет імені Данила Галицького;  
Кафедра внутрішньої медицини № 2  
к. мед. н, асистент кафедри  
79016 Україна, м. Львів, вул. Пекарська, 576  
zenvadim@gmail.com  
ORCID ID: <https://orcid.org/0000-0002-4377-452X>

#### Information about authors

##### L. V. Besh

Danylo Halytsky Lviv National Medical University Department of Pediatrics No. 2  
Doctor of Medical Sciences, professor

##### O. M. Besh

Danylo Halytsky Lviv National Medical University  
Department of Internal Medicine No. 2  
PhD, Assistant professor  
Dovholittia Medical Center,  
79016 Ukraine, Lviv, Pekarska str. 57b

##### O. O. Sorokopud

Danylo Halytsky Lviv National Medical University  
Department of Internal Medicine No. 2  
PhD, Associate Professor  
79016 Ukraine, Lviv, Pekarska str. 57b

##### M. O. Kondratiuk

Danylo Halytsky Lviv National Medical University;  
Department of Internal Medicine No. 2  
PhD, Associate Professor  
79016 Ukraine, Lviv, Pekarska str. 57b

##### O. R. Slaba

Danylo Halytsky Lviv National Medical University;  
Department of Internal Medicine No. 2  
PhD, Assistant professor  
79016 Ukraine, Lviv, Pekarska str. 57b

##### V. V. Zenin

Danylo Halytsky Lviv National Medical University;  
Department of Internal Medicine No. 2  
PhD, Assistant professor  
79016 Ukraine, Lviv, Pekarska str. 57b

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