**STUDY OF THE ROLE OF THE STRESS SYSTEM**

**IN THE DEVELOPMENT OF SEVERE FORMS OF PSORIASIS (CASE REPORT)**

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Up to the present day psoriasis remains one of the most urgent problems of modern dermatology. Its high share (up to 15 %) among other skin lesions, multifactorial aetiology, chronic recurrent course, psychosocial disadaptation of patients, incomplete knowledge of the mechanisms of development necessitate further studies of the disease pathogenesis.

The dependence of the clinical course of psoriasis and morphofunctional state of the skin upon the effect of different environmental factors, namely stress ones, as well as dysfunction of the hypothalamus, metabolic disturbances in hormones of the peripheral internal secretion glands in patients point out to an abnormality of adaptation mechanisms [2, 12, 13, 14]. Stress is known to be a provocative and aggravating factor of the course of psoriasis in 20-80 % of cases, as it follows from studies of Ukrainian researchers [7].

The stress response is based on an activation of the complex of mechanisms, which realize (stress-realizing) and limit (stress-limiting) it. The stress system is a sophisticated regulatory complex, which coordinates homeostasis in normal conditions and plays a key part in activating and coordinating changes in the body. This system consists of the central and peripheral links, which include components of the nervous, endocrine and immune systems that in this way provide the general adaptive response of the organism. The conjugated block of the hypothalamus and hypophysis is the central link of the stress-realizing system, its peripheral one consisting of the sympathoadrenal system and components of the endocrine system (the hypothalamic-pituitary-adrenal axis) [4, 11, 12].

The reaction of the organism in response to changes in its homeostasis was first described by Canadian physiologist Hans Selyeу in 1936. He termed this state the stress response and characterized it as the general adaptive syndrome or general nonspecific neurohumoral response of the organism to any requirement to it.

Also urgent remains a relationship of endocrine and immune changes in the development of psoriasis. A years-long chronic course of the disease affects functions of the nervous, endocrine and immune systems.

The purpose of the present work was to investigate the cause-effect mechanism of an exacerbation, progression or formation of severe forms of the disease as well as changes in the course of cutaneous psoriatic manifestations with revealing of the role of the stress-response in their development by analysis of dynamic peculiarities in the course of psoriasis using a clinical case in the anamnesis as an example.

The observation involved patient A., who was born in 1986 and, according to his case history, had been ill with psoriasis since 2011. The scope of diagnostic measures corresponded to the clinical protocol of medical aid for psoriasis, approved by the Ministry of Health of Ukraine in 2016. The study included the patient’s psychosomatic state, values of some metabolic processes and stress-realizing immune-neuroendocrine system (cortisol level, ACTH, cytokine profile, state of the immune system) in the beginning of the disease progression in the form of palmoplantar pustulosis against a background of extensive psoriasis and during periods of remission of skin manifestations.

Mental characteristics of the examined patient were studied on the basis of a diagnostic interview and the obtained data were verified with use of standardized experimental-psychological techniwues for revealing the level of neurological changes after Wassermann, the levels of state and trait anxiety after Spilberg-Khanin, and the level of depression self-rating by the Zung scale [8, 16]. The value of 60 % and higher was regarded as a high, i.e. clinically significant, level of neurotization. The level of anxiety below 30 points was considered to be low, 31-45 points – moderate, 46 points and more – high. A high level of state anxiety was regarded as clinically significant. If the value by the Zung scale was 50 points and lower, the state “without depression” was diagnosed, 51-59 points revealed “mild depression”, 60-69 points detected “masked depression” or the state of subdepression, 70 points and more pointed to “true depression”. Mild, “masked” and true depressions were considered to be clinically significant for the course of psoriasis.

Proper test systems were used in order to reveal the following values of: protein metabolism – blood serum levels of total protein, urea and albumins, percentage ratio of protein fractions, thymol test level; lipid metabolism – content of total lipids, β-lipoproteins, triglycerides and cholesterol; carbohydrate metabolism – glucose concentration; activity of alanine and aspartate aminotransferases (ALT, AST), blood serum amylase; content of bile pigments, bilirubin concentration.

The levels of T and B lymphocyte subpopulations in the patient with psoriasis were detected in compliance with the instruction for using erythrocytic diagnostic agents Anti-CD3, Anti-CD4, Anti-CD8, Anti-CD16 and Anti-CD22 (“Granum”, Ukraine) in order to reveal human T and B lymphocyte subpopulations.

Concentrations of total immunoglobulins of classes M (IgM) and G (IgG) in blood serum were revealed by ELISA with help of such kits as “Total IgM – ELISA – BEST” and “Total IgG – ELISA – BEST” (“Vector-BEST”, Russia).

The content of IL-1β, IL-8, IL-10, IL-17 and TNF-α in the patient’s blood serum was studied following the techniques and instruction with help of proper test systems (“Vector-BEST”, Russia) on the basis of the sandwich method of enzyme-linked immunosorbent assay.

Concentrations of ACTH and cortisol in blood plasma were revealed using proper reagent kits “ACTH-(Cortisol)-ELISA-BEST” (“Vector-BEST”, Russia), the above being based on the technique of enzyme-linked immunosorbent assay with use of monoclonal antibodies.

**Results and discussion**

Let us analyse peculiarities in the course of psoriasis on the example of a clinical case in the anamnesis with the subsequent revealing of the role of the stress-response during an exacerbation, progression or formation of severe forms of the disease.

Patient A. came to a dermatologist in November of 2016 for a regular examination as a follow-up case since 2011, when the following initial diagnosis was made: diffuse vulgar plaque psoriasis with a moderate degree of infiltration, the steady stage, a moderately recurrent course, chronic gastritis, chronic cholecystitis. The patient attributed the onset of his disease and subsequent exacerbations of the pathological skin process to frequent nerve strain. Allergic responses to medicines (Paracetomolum, Thiotriazoline, salicylic ointment) and foodstuffs (oranges, eggs, peanuts) developed often. Inheritance for psoriasis was tainted on the paternal line. The patient abused alcohol. He developed exacerbations once during two years in the winter period, but had not observed any clear periodicity of manifestations since 2014. He underwent outpatient and inpatient treatment several times according to protocols. The periods of exacerbation lasted from 2 to 3 months. Patient A. was hospitalized on November 27, 2016 with complaints about extensive eruptions on the skin of his scalp, trunk, upper and lower extremities as well as pronounced itching, skin contractions in the areas of eruptions, feeling unwell and sleep disturbances. On examination, the skin of his scalp, all trunk surfaces, upper and lower extremities revealed extensive oedematous-infiltrative erythematous foci as well as pustular eruptions on his palms. The whole surface of the eruptions was covered with white-silver desquamation, which easily fell off. The psoriatic triad was positive. Nail plates had numerous punctate impressions (“thimble symptom”) and transversal furrows. Psoriasis Area Severity index (PASI) = 54.2. According to the results of the clinical-laboratory examination, the following diagnosis was made: diffuse vulgar psoriasis with a torpid course and a sharply expressed degree of infiltration, palmar pustular psoriasis, its progressive stage with a moderately recurrent course; psoriatic onychodystrophy; reactive hepatitis. Hence, psoriasis was classified as severe. Taking into consideration the data of his anamnesis and results of the clinical-laboratory examination (Tables 1-2), the patient was recommended cytostatics – methotrexate, narrowband phototherapy with 311 nm of the whole body, external therapy with glucocorticosteroids.

Laboratory examinations were carried out in the dynamics of the suggested treatment. In the process of the recommended therapy the changed values of the patient’s general blood analysis and biochemical examination normalized almost completely, except for ESR level and AST. But despite the clinical stabilization in the activity of the cutaneous psoriatic process the results of the obtained data on the stress-realizing immune-neuroendocrine system revealed unsatisfactory functioning of the patient’s adaptive response and necessitated revision of the treatment protocol, particularly the adequate corrective therapy. The patient stayed 18 days at the dermatological department and was observed as an outpatient up to total 48 days. The period of treatment demonstrated the following dynamics of eruptions: decrease of desquamation on the 4th day, decrease of infiltration from the 8th one, marked paleness of eruption elements on the 11th-12th days, clear regression of psoriatic elements from the 19th one. Besides, pustules on the palms regressed on the 19th day too. Complete oral prophylaxis and tonsillectomy were performed. The patient refused to drink alcohol. During his regular prophylactic medical examination in February of 2017 the patient revealed complete remission of psoriasis.

The patient’s psychosomatic state and stress-realizing immune-neuroendocrine system were studied at the onset of psoriasis progression, particularly during development of its severe stage (pustular psoriasis), and in the period of remission of skin syndrome. The psychosomatic state of the patient in the beginning of the development of the severe stage and at the period of remission of the skin process (during a double survey in the dynamics of treatment) and the above state in healthy people significantly differed, particularly: neurotization in the patient – 74.3 ± 0.5, at the stage of remission of the skin process – 57.4 ± 0.2, while that of healthy people was 4 ± 0.1; state anxiety, respectively – 48 ± 0.3, 32 ± 0.8 and 7.8 ± 0.2; trait anxiety, respectively – 79.1 ± 0.9, 59.1 ± 0.4, 7.3 ± 0.5. Life quality indicators: physical activity – 34.2 ± 0.3, 40.8 ± 0.5 in the patient and 96.2 ± 1.2 in healthy people; social activity – 23.5 ± 1.7, 31.7 ± 1.11 in the patient and 86.9 ± 0.3 in healthy people; mental health indicator, respectively – 24.12 ± 1.7, 32.3 ± 1.7 and 58.9 ± 1.4. These data reveal that the patient had a significantly disturbed psychoemotional state, which hampered him in social adaptation and self-realization as an individual.

The concentrations of trigger cytokines IL-1β, IL-8, IL-10, IL-17 and TNFα, that of stress hormones – ACTH and cortisol as well as the state of cellular-humoral immunity (CD3, CD4, CD8, CD16, CD22, immunoregulatory index (ІRІ); levels of IgМ, IgG) were revealed in the patient’s blood serum during his examination. A reliable increase of concentrations of all stress response mediators was detected, it demonstrating an intension of stress-realizing mechanisms in the patient despite clinical stabilization of his skin process. In our opinion, self-depreciation of the patient as for the social implication of his personality acts as the stress factor in this situation. Marked changes in the studied values of the stress-realizing immune-neuroendocrine system developed as a response to the damage of the functional-psychological kind. Findings of our clinical studies confirm an activation of the stress system in psoriasis [7, 10, 15]. For example, particularly reliable are increases of IL-8, IL-10, TNFα, АCTH and cortisol levels simultaneously with significantly decreased levels of IL-1β and IL-17. Hence these indices play their part in the development of psoriasis and its severe forms, their various effects necessitating further studies. We believe that IL-1β, IL-8, IL-17 and TNFα are key mediators of the stress-realizing immune-neuroendocrine system. The above cytokines are expressed mostly in those areas, which are responsible for autonomic and endocrine regulation (hypothalamus, hippocampus) and can modulate activity of hormone-producing cells. Hence, being activated, the system of IL-1β, IL-8, IL-17 and TNFα causes a complex stress-realizing response of the immune-neuroendocrine system.

The levels of each of the above mediators of the immune-neuroendocrine system directly correlated with the severity of the patient’s dermatological state and the degree of his psychosomatic changes, thereby giving grounds for noticing their effect on the course of the disease. This fact confirms a damaging influence of the excessive stress response, which is a severe distress with cytotoxic and proapoptotic effects of cytokines and stress hormones [1, 2, 4], it being totally reflected on the clinical course of psoriasis and the patient’s social adaptation. A relation of the stress system mediators with the degree of psoriasis regression gives grounds to examine these indices as diagnostic criteria for revealing the degree of severity in the course of disease and use them in designing new therapeutic strategies. This patient’s example clearly demonstrates the function of the human regulatory system, aimed to maintain its homeostasis both at norm and in pathology. The regulatory system function is expressed by a close interaction (especially during responses to stresses) of the immune, nervous and endocrine components (the “homeostatic triangle”) following the principle of mutual regulation, which is provided by neuropeptides, hormones and cytokines [1, 4, 7, 13, 15]. Therefore an initial damage of any subsystem of the immune-neuroendocrine system constitutes a risk of the development of dysregulatory pathology [9].

So, the stress response has a general course and irrespective of the cause of stress (mental strain, injury, childbirth, metabolic change in the body, burns, scalds, sepsis, etc.) is accompanied with a significant intension of the stress-realizing systems, the hypothalamic-pituitary-adrenal one in particular. The result of the deficit of stress-limiting mechanisms is as follows: the stress response, which is initially adaptive, begins to take part in mechanisms of the pathological process [3, 5, 6]. This fact makes urgent further studies of the state of the stress-realizing immune-neuroendocrine system in psoriasis and expediency of such therapy, which is aimed at limitation of an excessive stress response.

Table 1. Dynamics of biochemical values

|  |  |  |
| --- | --- | --- |
| **Index** | **Norm** | **Date** |
| **28.11.2016** | **25.12.2016** |
| Albumins, % | 56.6–66.8 | 51.5 | 60.6 |
| Total protein, g/l | 65–85 | 69.0 | 76.0 |
| Globulins, % | 43.4–33.2 | 48.5 | 39.4 |
| α1, % | 3.5–6.0 | 4.2 | 5.8 |
| α2, % | 6.9–10.5 | 12.2 | 8.0 |
| β, % | 7.3–12.5 | 8.7 | 9.2 |
| γ, % | 12.8–19.0 | 23.4 | 16.4 |
| Total bilirubin, µmol/l | 8.5–20.8 | 21.0 | 17.8 |
| Glucose, mmol/l | 3.5–5.7 | 4.7 | 4.1 |
| Thymol test, units | 0–4 | 4.6 | 2.1 |
| ALT, µkat/l | 0.028–0.190 | 0.320 | 0.190 |
| AST, µkat/l | 0.028–0.190 | 0.250 | 0.210 |
| Amylase,mg/h × ml | 12–32 | 17.0 | 23.0 |
| Urea, mmol/l | 2.5–8.3 | 5.7 | 5.4 |
| Total lipids, g/l | 3.5–8.0 | 4.7 | 5.5 |
| β-lipoproteins, units | 35–55 | 27 | 35 |
| Triglycerides, mmol/l | 0.55–1.65 | 0.98 | 0.80 |
| Cholesterol, mmol/l | 4.65–6.46 | 7.5 | 5.0 |
| Seromucoids, units | 0.13–0.2 | 0.09 | 0.13 |

Table 2. Dynamics of some values of the stress-realization immune-neuroendocrine system

|  |  |  |
| --- | --- | --- |
| **Index** | **Results of studies** | **Value of healthy people**  |
| **28.11.2016** | **25.12.2016** | **%** |  **Abs. count** |
| **%** |  **Abs. count** | **%** |  **Abs. count** |
| Dynamics of some values of cellular immunity |
| Leukocytes, g/l |  | 5.0 |  | 7.2 |  | 4.0-8.0 |
| Lymphocytes, g/l | 35 |  | 21 |  | 18-40 | 1.2-3.5 |
| CD3/Т lymphocytes, g/l | 63 | 1.10 | 58 | 0.88 | 50-80 | 0.6-2.5 |
| CD4/Т helpers, g/l | 30 | 0.53 | 37 | 0.56 | 33-46 | 0.45-1.20 |
| CD8/Т cytotoxic leukocytes, g/l | 33 | 0.58 | 21 | 0.32 | 17-30 | 0.25-0.75 |
| CD16/natural killers, g/l | 16 | 0.28 | 22 | 0.33 | 12-23 | 0.20-0.50 |
| CD22/В lymphocytes, g/l | 18 | 0.32 | 25 | 0.38 | 17-31 | 0.20-1.10 |
| Immunoregulatory index (IRI) | 1.75 |  | 1.76 |  | 1.4-2.1 |  |
| Dynamics of some values of humoral immunity |
| Total immunoglobulins of class М (IgM), mg/ml | 2.6 |  | 1.8 |  | 0.5-2.0 |  |
| Total immunoglobulins of class G (IgG), mg/ml | 51.4 |  | 20.6 |  |   5.3-16.5 |  |
| Dynamics of some values of the hormonal system |
| ACTH, pg/ml | 128.0 |  | 59.8 |  | 9-52 |  |
| Cortisol, nmol/l | 903.8 |  | 281.5 |  | 190-690 |  |
| Dynamics of some values of the cytokine profile |
| Interleukin-1β (IL-1β) | -4.2 |  | 0.7 |  | 0-11 |  |
| Interleukin 8 (IL-8) | 215.0 |  | 64.8 |  | 0-10 |  |
| Interleukin 10 (IL-10) | 38.3 |  | 24.6 |  | 0-31 |  |
| Interleukin 17 (IL-17) | -4.4 |  | 0.5 |  | 0-5 |  |
| Tumor necrosis factor α (TNFα) | 18.2 |  | 19.8 |  | 0-6 |  |

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The purpose of the study was to follow the casual mechanism of exacerbation, progression and formation of severe forms of psoriasis, as well as the progression of cutaneous manifestation of psoriasis with the definition of the role of stress response in their development by analyzing features of the psoriasis dynamics on the example of reviewing clinical case in anamnesis.

Materials and methods. Examination of the psychosomatic condition and stress-making immunoneuroendocrine system of the patient with psoriasis was conducted at the beginning of disease and in the remission period of psoriasis. In the patient’s blood serum the concentration of trigger cytokins (IL-1β, IL-8, IL-10, IL-17, TNFα), stress hormones – ACTH and cortisol, the states of cell-humoral immunity (CD3, CD4, CD8, CD16, CD22, immunoregulatory index, Levels of IgM, IgG) were identified.

Results and discussion. The results of the study confirm the activation of the stress-system during psoriasis, in particular by elevation of levels of IL-8, IL-10, TNFα, ACTH, cortisol along with the decrease of levels of IL-1β, IL-17, which indicates the tension of the stress-making mechanisms of the patient with psoriasis in spite of clinical stabilization of cutaneous process.

Conclusions. Therefore the above mentioned indications appear to be key mediators of stress-making immunoneuroendocrine system and play an equivocal role in the development of the severe form of psoriasis. Their diverse effects require further investigation.

Key words: psoriasis, ACTH, cortisol, stress syndrome, immune disorders.

**ИЗУЧЕНИЕ РОЛИ СТРЕСС-СИСТЕМЫ В РАЗВИТИИ ТЯЖЕЛЫХ ФОРМ ПСОРИАЗА (Клинический случай)**

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Цель работы – проанализировать особенности динамики течения псориаза на примере рассмотрения клинического случая в анамнезе, причинно-следственный механизм обострения, прогрессирования и формирования тяжелых форм заболевания, а также прогрессирования кожных псориатических проявлений с определением роли стресс-реакции в их развитии.

Материалы и методы. Проведено исследование психосоматического состояния больного и иммунонейроэндокринной системы в начале заболевания псориазом и в периоде ремиссии кожного процесса. В сыворотке крови пациента определяли концентрации триггерных цитокинов (IL-1β, IL-8, IL-10, IL-17, TNFα), стрессорных гормонов – АКТГ и кортизола, состояния клеточно-гуморального иммунитета (CD3, CD4, CD8, CD16, CD22, иммунорегуляторный индекс, уровня IgM, IgG).

Результаты и обсуждение. Данные клинического исследования подтверждают активацию стресс-системы при псориазе, в частности повышение уровней IL-8, IL-10, TNFα, АКТГ, кортизола с одновременно сниженным уровнем IL-1β, IL-17, что свидетельствует о напряженности стресс-реализующих механизмов при псориазе, несмотря на стабилизацию кожного псориатического процесса.

Выводы. Таким образом, данные показатели являются ключевыми медиаторами стресс-реализующей иммунонейроэндокринной системы и играют неоднозначную роль при развитии тяжелых форм псориаза. Их разнообразные эффекты требуют дальнейшего изучения.

Ключевые слова: псориаз, АКТГ, кортизол, стресс-синдром, иммунные нарушения.

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