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Role of certain immune-endocrine parameters in the pathogenesis of psoriatic arthritis

Psoriasis is a life-long chronic autoimmune disease characterized by thick scaly skin lesions and often associated with severe arthritis. At the present stage, psoriasis is considered to be a systemic disease that affects not only skin but also joints of patients and is accompanied by possible development of typical comorbid states (cardiovascular pathology, chronic inflammatory intestinal canal diseases, and metabolic syndrome).

Objective — to improve the diagnosis of arthropathic psoriasis (AP) taking into account some of the most important indicators of the immune-endocrine system and features of the disease course to specify their role in the pathogenesis of the disease and to develop the system of integrated therapy.

Materials and methods. A total of 178 AP patients have been systematically examined that had varying severity of process development, generalization and intensity of skin and osseous-articular apparatus damage, the presence of associated pathology. Additional instrumental studies, determination of biochemical, serological parameters and an assessment of stress-induced immune-endocrine system have been conducted in AP patients. The content of trigger cytokines (IL-1β, IL-8, IL-17, IL-22) in blood serum, stress hormones (ACTH, cortisol), cellular and humoral immunity condition ($CD3^+$, $CD4^+$, $CD8^+$, $CD16^+$, $CD22^+$, IgM and IgG levels) have been studied.

Results and discussion. The clinical course and characteristic features of AP instrumental tests are extremely versatile. Regardless of the disease duration period, we have detected in blood serum of AP patients probable decrease in parameters of cellular immunity ($CD3^+$, $CD4^+$, $CD8^+$-fraction of T-lymphocytes, $CD22^+$-fraction of B-lymphocytes) and compensatory increase in $CD16^+$ of T-cells, decrease in parameters of cytokines (IL-1β, IL-8, IL- 17, IL-22), stress hormones (cortisol, immunoglobulins IgM, IgG, and CIC), which indicates tension of their stress-induced mechanisms even despite occasional clinical stabilization of skin and articular process.

We have offered and tested regiments to treat AP patients, which involve differential application within the integrated therapy of nonsteroidal anti-inflammatory medications (etoricoxib 30—60 mg 1 time daily/diclofenac 75 mg daily), disease-modifying medications (sulfasalazine EH from 500 mg to 2 g daily/methotrexate 7.5—10 mg/week), lyophilised dialysate of leukocytes.

Conclusions. The analysis of specific features of the AP clinical course and data of integrated studies allows identifying the probability of manifestation or persistence of the pathological psoriatic articular process. The improvement of AP patients diagnostics taking into account some of the most important indicators of the immune-endocrine system and specifics of the disease course contributed to the improved therapy and mended quality of life of patients.

Keywords

Arthropathic psoriasis, indicators of the immune, endocrine system, pathogenesis, diagnosis.

Psoriasis is a life-long chronic autoimmune disease characterized by thick scaly skin lesions and often associated with severe arthritis. At the present stage, psoriasis is considered to be a systemic disease that affects not only skin but also joints of patients and is accompanied by possible development of typical comorbid states (cardiovascular pathology, chronic inflammatory intestinal canal diseases, and metabolic syndrome) [1, 3, 4, 13]. Psoriasis affects about 2 % of population. In 30—40 % of occurrences arthropathic psoriasis (AP) is diagnosed and leads to 11—19 % of disability cases development [2, 6]. Arthropathic psoriasis is a chronic inflammatory autoimmune condition characterized by inflamed joints. AP can affect the large joints such as the knees and shoulders but also may

also occur in joints like the fingers, toes, back or pelvis [7, 14]. Symptoms usually start between ages 30 and 50 and can lead to mild symptoms or chronic inflammation that may result in joint damage if not treated appropriately. Men and women are equally at risk [5, 12].

According to many researchers [2, 11, 12], immunometabolism has emerged as a potent mechanism elucidating the etiopathogenesis of psoriasis, offering novel specific targets to diagnose and treat psoriasis early. Besides, decreased levels of cortisol were found in patients with stress and exacerbated psoriatic lesions that can affect the immune and endocrine systems [6, 8, 9].

Objective — is to improve the diagnostics of AP patients taking into account some of the most important indicators of the immune-endocrine system and features of the disease course to specify their role in AP pathogenesis and to develop the system of integrated therapy of patients whose locomotor system is affected due to psoriasis.

Materials and methods

A total of 178 AP patients have been systematically examined, 72 (40.4 %) female and 106 (59.6 %) male. We have examined AP patients with varying severity of process development, generalization and the severity of skin and osseous-articular apparatus damage, the presence of associated pathology. The diagnosis of AP was verified under the diagnostic criteria of the Institute of Rheumatology of RAMS. All patients with suspected or proved AP had their damaged joints examined radiologically (ultrasonography if necessary). Additional level of T- and B-lymphocytes subpopulations in patients with AP was determined under the guidelines on the application of erythrocyte diagnostic preparations to detect human T- and B-lymphocytes subpopulations «Anti-SD 3», «Anti-SD 4», «Anti-SD 8», «Anti-SD 16», «Anti-SD 22» produced by RDPF Granum LLC (Kharkiv). The concentration of general immuniblibulines of M (IgM) and G (IgG) classes in blood serum was determined by immune-enzyme analysis using «IgM (IgG) general — IFA — BEST» set produced by CJSC «Vector-Best — Ukraine». The content of IL-1β, IL-8, IL-17, IL-22 in blood serum was studied in accordance with the techniques and guidelines using appropriate test systems (CJSC «Vector-Best — Ukraine») which are based on the sandwich-method of solid phase immune-enzyme analysis. The quantitative determining of cortisol concentration in blood plasma was performed using the appropriate reagent sets, i.e. «Cortisol — IFA — BEST» which are based on the method of solid phase immune-enzyme analysis with the application of monoclonal antibodies.

Results and discussion

Based on the statistical data analysis, it was established that over the past 20 years the number of registered cases of psoriasis among the population of Lviv region has increased by 1.4 times against the growth by 2.2 times in respect of the newly established cases. An increase in the incidence rate by 1.3 times among children and adolescents and twofold prevalence of hospitalization of urban male population was determined. This situation may be caused by the accumulation of several factors such as bad ecological situation in Ukraine, insufficient level of material and living conditions that leads to psychoemotional stress and, as the result, to decreasing of clinical remission period in patient and more frequent relapses.

In 113 (63.48 %) out of 178 examined AP patients joints were damaged in 5—15 years after the onset of skin psoriatic process. In 85 (47.75 %) cases the dependence of the onset of joint damage with the subsequent manifestations of psoriatic skin rash was detected. According to medical history data, the examined patients typically associated the onset of psoriatic skin and joints damage with hereditary 32 (17.98 %), stress 67 (37.64 %), alcoholic and toxic 17 (9.55 %), tonsillar 16 (8.99 %), mono- and polytraumatic 35 (19.66 %) factors, others 11 (6,18 %) (Fig. 1).

In 126 (70.78 %) AP patients the prevalence of generalized skin psoriatic process with typical (84.26 %), large plaque rash (38.20 %), moderate infiltration degree (60.1 %), moderate severity (65.73 %), mixed type (62.92 %), inpatient stage (57.30 %) and frequent recurrent course (48.31 %) was observed.

It has been established that in 113 (63.48 %) AP patients joints damage occurred in 5—15 years after the onset of skin psoriatic process. In 70.22 % of examined patients the prevalence of generalized skin psoriatic process with typical (84.26 %), moderate infiltration degree (62.92 %) (Fig. 2, 3), frequent recurrent course (43.82 %), nails psoriatic damage

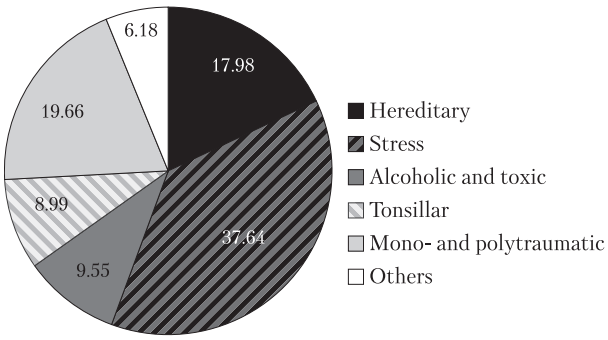

Fig. 1. **Factors that provoked the development of psoriasis, %**

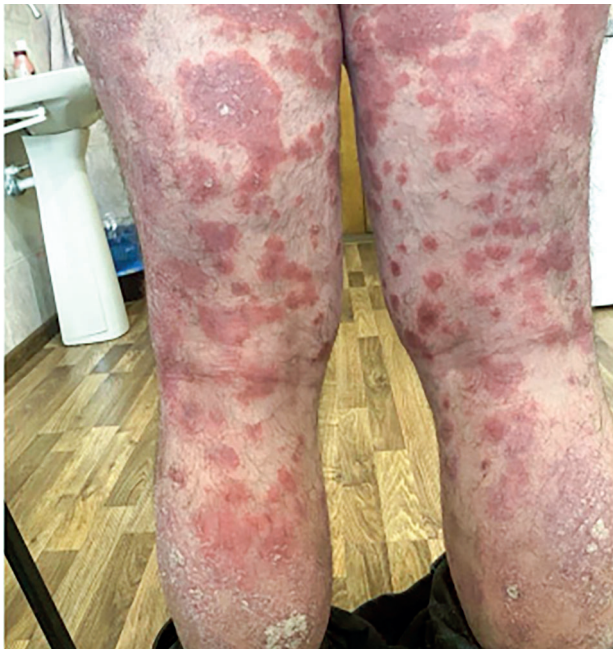

Fig. 2. **Patient K., 58 years old. Arthropathic psoriasis**

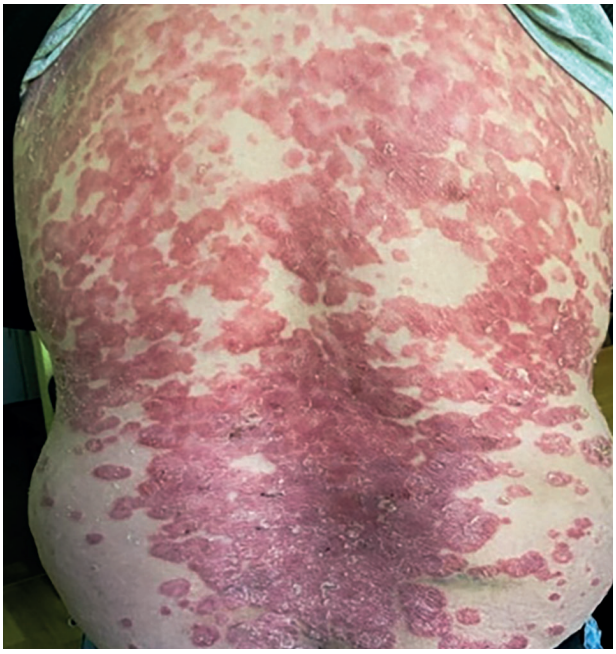

Fig. 3. **Patient M., 47 years old. Generalized skin psoriatic process**

Fig. 4. **Patient A., 42 years old. Nails psoriatic damage**

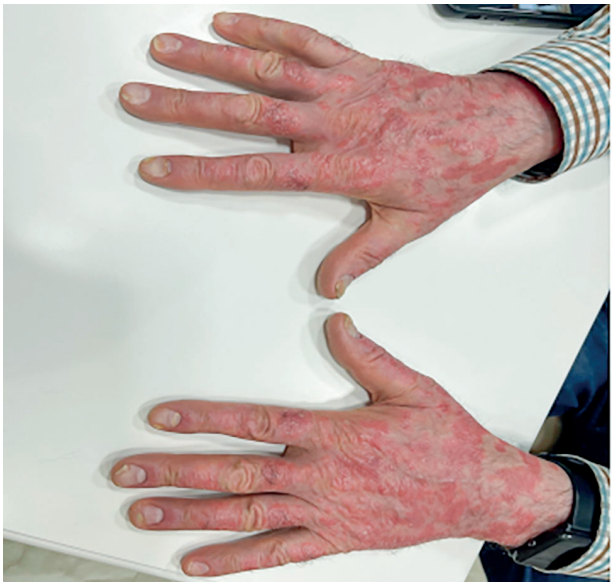

Fig. 5. **Patient D., 55 years old. Polyarthritis complicated with the damage of small joints of hands**

(Fig. 4), and polyarthritis complicated with the damage of small joints of hands (Fig. 5) or feet was observed (79.78 %).

Upon conducting functional tests (in order to determine sacroilitis — Kushelevsky 1—2, Patrick, Mennel and spondylitis — Shober, Thomayer), sacroilitis has been revealed and further instrumentally confirmed in 7 (3.93 %) cases and spondylitis of thoracic and lumbar sections in 12 (6.74 %) cases. Using the RAIS index, in 89.4 % of patients it has been verified moderate-severe and severe dermatosis course. A significant impact of AP on the quality of life of patients per the DLQI index has been recorded in 57.30 %, and very significant in 48.31 %. A pronounced correlation between the increase in joints functional deficiency, the AP course duration and the deterioration in the quality of life of patients has been established. A high degree of polyarthritis detection rate complicated with the damage of small joints of hands or feet associated with a functional insufficiency of average degree of activity (57.30 %) though the preservation of pro-

fessional ability has been diagnosed in 42.13 % of patients.

In this context we have determined pathognomonic signs of AP, which include simultaneous psoriatic damage of skin (100 %) and nails (73.21 %); asymmetric (82.4 %) mono- or oligoarthritis (68.32 %) mainly of peripheral joints and especially associated with the hand DIPJ damage (92.18 %); osteolysis (87.43 %); negative reaction for rheumatoid factor (97.22 %).

We have pathogenetically grounded the primary localization of pathological joint process in AP patients in the areas of increased traumatization of tendon-ligamentous apparatus and its relationship with nails psoriatic damage. Therefore, ultrasound diagnostics and MRI examination of joints for the purpose of determination of periarticular and articular damages is justified since in 10.71 % of examined patients enthesopathy and osteitis in the absence of abnormal articular X-ray changes have been detected by ultrasound diagnostics and MRI. In our opinion, osteitis in psoriatic patients signals an early premonitory symptom of the AP development.

During radiological examination of patients with AP it was detected 88 (49.44 %) cases of AP and 66 (37.08 %) cases of deforming AP, at that, in 120 (67.42 %) of cases AP was the dominant disease on clinical picture in the form of poly- or periarthritis of distal interphalangeal joints, at that, in 19 (10.67 %) of cases it was associated with axial affection of spine. At early stages of AP development using radiological examination the following facts were accurately defined more frequently than the others: non-uniform narrowing of joint gap, osteoporosis in bone epimetaphys area, erosions of distal flanges of feet and hands. In the case of progressing — partial or total destruction of closing plates with prevailing osteo-destructive (osteolysis, ankylosis) and osteo-proliferated (hyperostosis, periostitis) pathological processes over osteoporosis.

In 107 (60.11 %) AP patients the presence of inflammatory biochemical serum and cholecystobiliary syndromes has been testified, which indicates metabolic character of the disease course. The analysis of laboratory examinations indicates the decreased number of thrombocytes, expressed hypoalbuminemia, hypergammaglobulinemia. In 1/3 of patients with AP anaemia was identified as well as increasing of BSR within the limits of 15—20 mm/h, from 21 to 40 mm/h — in 37 (20.79 %) of patients, more than 40 mm/h — 20 (11.24 %). The increased glucose level was identified in 44 (24.71 %) of patients, cholesterol and LDL — in 120 (67.41 %), creatinine — in 83 (46.63 %). Alkaline phosphatase and its bone izoenzyme activity were within the limits of normal values except the patients who have been suffering from the disease for more than 20 years. This means that alkaline phosphatase activity exceeds the norm more than 2.3—2.5 times and bone izoenzyme alkaline phosphatase decreased in 2.6—2.7 times. Creatinine content in blood serum was lower than the norm in 86 (48.31 %) of patients notwith standing the duration of the disease.

Calcium concentration in blood serum was within the norm limits. Phosphorus content tended to be increased in 1.2—1.3 times notwithstanding the duration of AP, thus testifying the disorder in catabolic and synthetic reactions.

Indices of C-reactive protein were as follows: negative «–» — in 54 (30.34 %) of patients, «+» — in 77 (43.26 %), «++» — in 31 (17.42 %), «+++» — in 11 (6.18 %) and «++++» — in 5 (2.81 %) of cases.

It has been determined that the occurrence of pathological immune-endocrine process in all variants of AP course was triggered by a possible blood serum decrease ($p < 0.01$) of immunocompetent cells of phenotype $CD3^+$ by 50 %, $CD\ 22^+$ or B-lymphocytes by 46.63 %, moderate decrease of $CD4^+$ by 12.36 %, $CD8^+$ by 19.66 % and increased content of $CD16^+$ by 18.54 %; increased levels of cytokines IL-1β by 5—11 times, IL-8 by 60 times, IL-17 by tenfold, IL-22 by 5 times, cortisol stress hormone by twofold, IgG by 5 times and immunoglobulins IgM by threefold, which testify the fact of tension of stress-induced mechanisms in patients even at the stage of clinical stabilization of skin and joint process. A statistically significant increase of the above cytokine concentration in blood serum (by more than 2—3 times) and in synovial fluid (by more than 2—5 times against the respective values in blood serum; $p < 0.05$) during the first months starting from the PD joint syndrome onset can serve as an additional diagnostic criterion for early AP diagnostics.

It has been set that the character of correlation between changed indicators of immune-endocrine system in AP patients indicated the autoimmune nature of the disease chronicity and development. It has been justified that decreased levels of cytokines IL-1β, IL-8, IL-17, IL-22, cortisol, IgM, IgG are the key mediators of the stress-induced immune-endocrine system since they cause inflammation and osteolysis on the one hand and regulate the processes of articular contractions formation on the other hand.

We have offered and tested regiments to treat AP patients, which involve differential application within the integrated therapy of nonsteroidal anti-inflammatory medications (etoricoxib 30—60 mg 1 time daily/diclofenac 75 mg daily), disease-modifying medications (sulfasalazine EH from 500 mg to 2 g daily/methotrexate 7.5—10 mg/week), lyophilised dialysate of leukocytes. This allows increasing the efficacy of treatment under statistically signifi-

cant recovery of changed indicators of clinical, laboratory and instrumental examination ($p < 0.05$), controlling of AP progression, preserving of workability and improving of the quality of life of patients. It is recommended to administer methotrexate as a part of integrated therapy in the event of mild cases, especially central AP, and comorbid cardiovascular pathology. In the event of moderate severity of peripheral AP complicated with pronounced contractures and digestive tract pathology it is recommended to administer sulfasalazine.

Conclusions

The analysis of specific features of the AP clinical course and data of integrated studies allows identifying the probability of manifestation or persistence of the pathological psoriatic articular process. The improvement of AP patients diagnostics taking into account some of the most important indicators of the immune-endocrine system and specifics of the disease course contributed to the improved therapy and mended quality of life of patients.

No conflict of interest.

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Роль окремих імуноендокринних показників у патогенезі артропатичного псоріазу

Псоріаз — пожиттєве хронічне автоімунне захворювання, що характеризується ураженням шкіри та часто асоціюється з важким артритом. На сучасному етапі псоріаз вважають системним захворюванням, яке вражає не тільки шкіру та суглоби, а часто супроводжується розвитком супутніх захворювань (серцево-судинної патології, хронічних запальних захворювань травного тракту, метаболічного синдрому).

Мета роботи — удосконалити діагностику артропатичного псоріазу (АП) з урахуванням окремих найбільш значущих імуноендокринних показників і особливостей клінічного перебігу, вивчити їхню роль у патогенезі захворювання та розробити алгоритм комплексної терапії.

Матеріали та методи. Нами було комплексно обстежено 178 хворих на АП з різною важкістю захворювання, генералізацією і вираженістю шкірних проявів, кістково-суглобового апарату, наявністю супутньої патології. Всім пацієнтам було проведено додаткові інструментальні дослідження, проаналізовано результати біохімічних і серологічних досліджень та показники стрес-індукованої імуноендокринної системи. Визначено рівні тригерних цитокінів (IL-1β, IL-8, IL-17, IL-22) у сироватці крові, гормонів стресу (АКТГ, кортизолу), стан клітинного та гуморального імунітету ($CD3^+$, $CD4^+$, $CD8^+$, $CD16^+$, $CD22^+$, IgM та IgG).

Результати та обговорення. Особливості клінічного перебігу і результати інструментальних досліджень у хворих на АП були надзвичайно різноманітними. Незалежно від тривалості захворювання у всіх хворих було виявлено вірогідне зниження показників клітинного імунітету ($CD3^+$, $CD4^+$, $CD8^+$-фракції Т-лімфоцитів, $CD22^+$-фракції В-лімфоцитів) та компенсаторне підвищення — $CD16^+$ Т-лімфоцитів, зниження рівня цитокінів (IL-1β, IL-8, IL-17, IL-22) та гормонів стресу (кортизолу, імуноглобулінів IgM, IgG, ЦІК), що вказує на напруженість їхніх стрес-індукованих механізмів навіть попри періодичну клінічну стабілізацію шкірного та суглобового процесу.

Розроблено та апробовано схеми лікування хворих, що передбачають диференційоване застосування в комплексній терапії нестероїдних протизапальних засобів (еторикоксиб 30—60 мг 1 раз на добу/диклофенак 75 мг на добу), хворобомодифікуючих препаратів (сульфасалазин ЕН від 500 мг до 2 г на день/метотрексат 7,5—10 мг/тиждень) та ліофілізованого діалізату лейкоцитів.

Висновки. Аналіз особливостей клінічного перебігу та даних комплексних обстежень дає змогу визначати ймовірність маніфестації або персистенції суглобового процесу у хворих на АП. Удосконалення діагностики АП з урахуванням окремих найбільш значущих імуноендокринних показників та особливостей клінічного перебігу захворювання сприяло удосконаленню терапії та поліпшенню якості життя пацієнтів.

Ключові слова: артропатичний псоріаз, показники імунної, ендокринної системи, патогенез, діагностика.

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