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ANALYSIS OF RISK FACTORS AND ASSESSMENT OF THE COURSE OF AVASCULAR NECROSIS OF THE FEMORAL HEAD IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Avascular necrosis of the femoral head is, although relatively rare, one of the most serious complications of systemic lupus erythematosus. The study focuses on searching for clinical and laboratory features of patients suffering from this complication, as well as on studying its consequences. Data from 149 patients with systemic lupus erythematosus were analyzed, 13 of whom were diagnosed with avascular necrosis of the femoral head. These patients were found to have significantly higher total doses of glucocorticoids, levels of cholesterol and uric acid in serum (at the time of diagnosis of the femoral head avascular necrosis); among clinical presentations, alopecia, lymphopenia and vascular pathology are more common. It has been established that the late age of systemic lupus erythematosus onset correlates with the early development of avascular necrosis of the femoral head. When analyzing the course of the disease, it was revealed that in 9 out of 13 patients, there was a need for arthroplasty of one or both hip joints. Thus, the issue of identifying risk factors and prevention of this complication is especially relevant; consequently, the description of even a small group of such patients may in the future help to study this problem comprehensively.

Key words: systemic lupus erythematosus, avascular necrosis of the femoral head, risk factor, hip arthroplasty.

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АНАЛІЗ ФАКТОРІВ РИЗИКУ ТА ОЦІНКА ПЕРЕБІГУ АВАСКУЛЯРНОГО НЕКРОЗУ ГОЛОВКИ СТЕГНОВОЇ КІСТКИ У ПАЦІЄНТІВ ІЗ СИСТЕМНИМ ЧЕРВОНИМ ВОВЧАКОМ

Аваскулярний некроз головки стегнової кістки є, хоча і відносно рідкісним, проте одним з найбільш серйозних ускладнень системного червоного вовчака. Дослідження присвячено пошуку клінічних та лабораторних особливостей пацієнтів, у яких розвилося дане ускладнення, а також вивченню його наслідків. Було проаналізовано дані 149 хворих на СЧВ, в 13 з яких діагностовано аваскулярний некроз головки стегнової кістки. Виявлено, що у цих пацієнтів достовірно вищі сумарна доза глюкокортикоїдів, рівні загального холестерину та сечової кислоти в сироватці крові (на момент діагностики аваскулярного некрозу головки стегнової кістки); частіше зустрічаються алопеція, лімфопенія та судинна патологія. Встановлено, що пізній вік дебюту СЧВ корелює з раннім розвитком аваскулярного некрозу головки стегнової кістки. При аналізі перебігу захворювання виявлено, що в 9 з 13 пацієнтів на певному етапі виникала необхідність в протезуванні одного чи обох кульшових суглобів. Таким чином, особливо актуальним є питання виявлення факторів ризику та профілактики даного ускладнення, тому опис навіть невеликої групи таких пацієнтів може в майбутньому допомогти всесторонньо вивчити проблему.

Ключові слова: системний червоний вовчак, аваскулярний некроз головки стегнової кістки, фактор ризику, протезування кульшових суглобів.

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Avascular necrosis of the femoral head (ANFH) is a type of osteonecrosis resulting from impaired blood supply to the proximal femur [2]. In the literature, it is also often referred to as "aseptic", emphasizing the absence of an infectious agent in the foci of necrosis. The primary cause is traumatic hip injuries (most often neck fractures and dislocations). The long-term therapy with glucocorticoids (GCs) is in second place [13]. Other causes include as follows: excessive alcohol consumption, autoimmune diseases, including systemic lupus erythematosus (SLE) [2], Legg-Calve-Perthes disease (the most common cause of ANFH in children) [8], sickle cell anemia [1], thrombophilia, Gaucher disease, caisson disease, radiotherapy and chemotherapy [4]. Pancreatitis, diabetes mellitus, HIV infection, myeloproliferative neoplasia, hyperparathyroidism, pregnancy, chronic kidney disease, hypercholesterolemia and smoking are also associated with an increased risk of this condition. Along with this, in approximately 30 % of cases of non-traumatic ANFH, the etiological factor cannot be identified [5, 9].

According to the meta-analysis conducted in 2017 the pooled prevalence of symptomatic avascular necrosis of bone in SLE was 8.96 % and femoral head was the most common location – 8.0 %. The main cause is considered to be long-term use of GCs; however, cases of the occurrence of this complication prior to the start of GCs administration have been described [6]. Although ANFH may complicate the course of primary antiphospholipid syndrome (APLS), an increased risk of its occurrence in patients suffering from SLE with positive antiphospholipid antibodies has not been proven yet [7].

Plain radiography of the pelvis and magnetic resonance imaging (MRI) of the hip joints are the most informative tools and most commonly used for diagnosing ANFH. There are several classification systems based on these methods. Ficat and Arlet system, developed in 1977 and modified in 1985, is one of the oldest, however, widely used in this direction. According to it, 4 stages of the process are distinguished. In the first and second stages, conservative therapy is used (bisphosphonates, vasodilators, antiplatelets, anticoagulants and lipid-lowering drugs) and non-radical surgical techniques, while the third and fourth stages are indications for total hip joint arthroplasty [4, 15].

Among all the complications of glucocorticoid therapy, ANFH is one of the most serious, forasmuch as in most cases it leads to the need for hip joint arthroplasty, which is connected with certain risks, especially in patients with burdened comorbid background. Therefore, the issue of identifying risk factors, preventing the development and early detection of ANFH, which have not been sufficiently studied at the present stage, is especially relevant. The main reason for this is that systemic lupus erythematosus belongs to orphan diseases, and ANFH is a relatively infrequent complication. Consequently, the description of even a small group of such patients may help to study comprehensively the issue outlined in the future.

The purpose of the study was to analyze the risk factors, features of the course and effectiveness of conservative treatment of avascular necrosis of the femoral head in patients with systemic lupus erythematosus.

Materials and methods. The medical records of 170 patients with SLE who had been treated at the SI "National scientific center "Institute of Cardiology, Clinical and Regenerative Medicine named after academician M.D. Strazhesko" National Academy of Medical Sciences of Ukraine in 2011–2020 were examined; a survey of 40 patients was conducted. 149 patients were selected for analysis, the data of which were quite informative. SLE was diagnosed according to the criteria of ACR (1997), SLICC (2012) or ACR/EULAR (2019).

*[ACR – American College of Rheumatology; SLICC – Systemic Lupus International Collaborating Clinics; EULAR – The European Alliance of Associations for Rheumatology].

ANFH was diagnosed in 13 patients (3 males, 10 females). All the cases were confirmed by MRI. The age at the time of diagnosis was 20–40.7 years (median – 27 years).

The control group amounted 35 patients with SLE, whose disease course was not complicated by ANFH, aged 15–54 years (median 30.8); they were comparable in terms of gender (7 males, 28 females), the age of SLE onset and the duration of the disease.

The informed consent to participate in the research was obtained from the patients who were surveyed. It was conducted in accordance with the basic bioethical norms of the Declaration of Helsinki of the World Medical Association "Ethical principles of medical research with human participation as an object of study". The study protocol was approved by the Committee on Bioethics and Deontology of the SI "National scientific center "Institute of Cardiology, Clinical and Regenerative Medicine named after academician M.D. Strazhesko" National Academy of Medical Sciences of Ukraine.

Statistical data analysis was performed using the statistical software packages Statistica 10 portable and the Microsoft Excel 2016, using non-parametric methods for small groups.

In both groups, the level of hemoglobin, platelets, leukocytes and lymphocytes in the blood; concentration of creatinine, uric acid, sodium, potassium, glucose, total cholesterol in serum; duration of glucocorticoid therapy, current and total doses in prednisolone equivalent (at the time of diagnosis of ANFH) were assessed. The results established in the study groups were compared using the Mann-Whitney U Test. Discrepancies were considered statistically significant at $p<0.05$. The results are represented as median, upper limit of the lower quartile, lower limit of the upper quartile (Me (25 %;75 %)).

Spearman's rank correlation coefficient was determined between the specified parameters, as well as the age of SLE onset and the duration of the disease. Correlation was considered significant at $p<0.05$.

In order to assess individual clinical manifestations as possible risk factors for ANFH, their frequency in each group was calculated. Based on this, 4-field tables were created, according to which the relative risk (RR), lower and upper limits (LL, UL) were calculated. The obtained result was considered reliable at LL>1.

Results of the study and their discussion. Among 149 patients, the course of the disease was complicated by ANFH in 13 (8.7 %), as well as unilateral avascular necrosis of the distal metaepiphysis of the femur and proximal epiphyses of the tibia and fibula was diagnosed in one patient. Such number of patients is compliant with the expectations, given the literature data on the prevalence of avascular bone necrosis in patients with SLE. This number includes 10 females, 3 males. The bilateral process was

observed in 11 patients; the unilateral process – in 2 patients. The average duration of SLE at the time of ANFH diagnosis is 7.6 years (8 months; 18 years).

All 3 antiphospholipid antibodies (lupus anticoagulant, antibodies to cardiolipin and Beta-2-glycoprotein) were positive in 2 patients, only lupus anticoagulant – in the other 2 patients. One patient confirmed smoking; all patients denied excessive alcohol consumption.

When comparing the parameters under consideration in the groups, it has been revealed that patients with ANFH have significantly higher total dose of glucocorticoids (1.86 times), the concentration of cholesterol (1.2 times) and uric acid (1.26 times) in serum (Table 1).

Table 1

Comparison of the main laboratory indicators and quantitative parameters of glucocorticoid therapy in patients with ANFH (experimental group) and without it (control group)

Index	Patients with ANFH	Control group	p
Hemoglobin (g/L)	123.0 (113.8;133.0)	116 (112;121)	0.61
Platelets (*10^9 cells/liter)	242.0 (226.0;268.5)	229.0 (180.5;285.3)	0.58
Leukocytes (*10^9 cells/liter)	5.2 (3,3;6,2)	4.5 (3.2;5.8)	0.79
Lymphocytes (*10^9 cells/liter)	1.98 (1.62;3.16)	1.49 (1.18;2.13)	0.095
Sodium (mmol/l)	141 (141.142)	142 (141.144)	0.33
Potassium (mmol/l)	4.3 (4.1;4.5)	4.3 (4.2;4.5)	0.67
Creatinine (mmol/l)	78.0 (72.5;90.5)	87.0 (75.8;103.8)	0.27
Uric acid (μmol/l)	*296 (283;336)*	*249.5 (225.5;304.5)*	*0.045**
Total cholesterol (mmol/l)	*6.2 (5.5;6.6)*	*5.3(4.2;6.1)*	*0.04**
Glucose (mmol/l)	4.5 (4.2;4.7)	4.5 (4.2;5.1)	0.56
GC dose – current (milligrams in terms of prednisolone)	11 (6;16)	10 (5;24)	0.96
GC dose – total (grams in terms of prednisolone)	26.9 (14.7;34.3)	11.9 (4.1;20.1)	*0.004**
Duration of GC therapy (years)	5.5 (2.0;10.1)	4.5 (0.9;8.9)	0.7

The data are presented as follows: Me (25 %; 75 %). * – significance of differences between groups (Mann-Whitney U Test).

While studying correlations, it has been established that there is a significant negative correlation between the age of SLE onset and the duration of the disease prior to ANFH onset (Spearman's rank correlation coefficient is equal to -0.83, $p<0.05$) (Fig. 1).

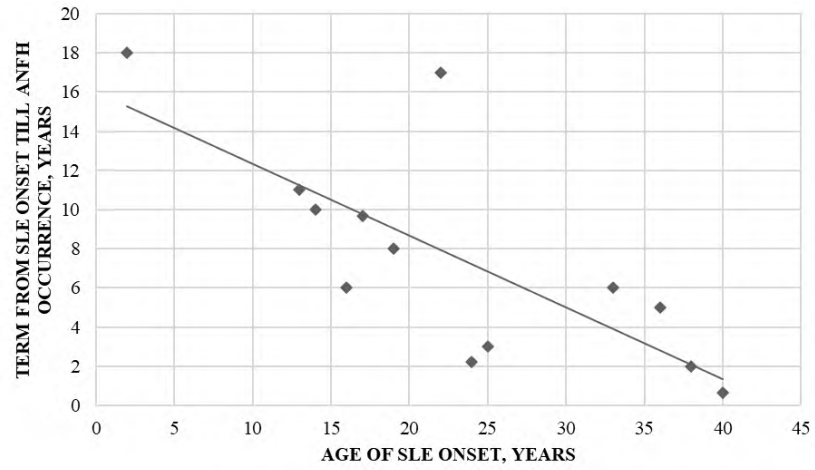

Fig. 1. Correlation between the age of the onset of systemic lupus erythematosus and the term from SLE onset till the occurrence of avascular necrosis of the femoral head.

Therefore, it can be concluded that the earlier is the age of SLE onset, the more time passes prior to the manifestation of ANFH, and vice versa, in patients with a later onset of SLE, ANFH occurs significantly earlier. Subsequently, the question has come up whether there are other reasons for such a predicted pattern. However, having calculated the correlation coefficients between the age of SLE onset and all other parameters, no significant correlations were found.

The next step was to determine the frequency of the main clinical manifestations among patients with and without ANFH and assess the relative risks. The presence of a manifestation in the anamnesis or at the time of diagnosing ANFH was taken into account. Presence of vascular pathology was of particular interest, forasmuch as it is the impairment of blood supply that underlies the pathogenesis of ANFH. From among patients with ANFH, the following vascular manifestations have been revealed, namely:

– antiphospholipid Syndrome – 3 patients;
– Raynaud's phenomenon – 3 patients;
– digital vasculitis – 1 patient;
– palmar capillaritis – 2 patients.

Such a number of each manifestation did not allow conducting a reliable statistical analysis; consequently, it was decided to use the total number of patients with vascular pathology for calculations. One of them has suffered from anti-phospholipid syndrome, Raynaud's phenomenon and palmar

capillaritis; thus, the total number of such patients is 7. fig. 2 shows the relative risks of ANFH in patients with or without main clinical manifestations.

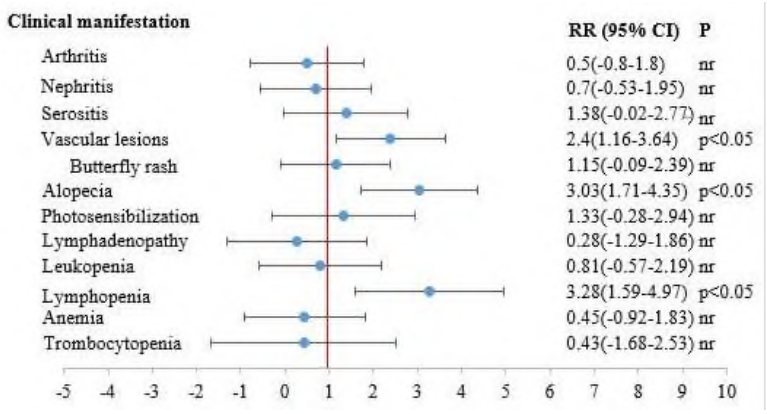

Fig. 2. Assessment of the clinical manifestations of systemic lupus erythematosus as possible predictors of the occurrence of avascular necrosis of the femoral head. (RR – relative risk; CI – confidence interval; nr – not reliable).

From the results obtained, it is seen that vascular pathology is definitely associated with an increased risk of ANFH. Regarding lymphopenia and alopecia, the data are contradictory and further study is needed. It is possible that these manifestations are related to high disease activity, which, in turn, leads to a higher risk of developing ANFH.

Bisphosphonates, vasodilators, statins, antiplatelet agents, and anticoagulants were used as conservative treatment of ANFH. The positive effect was observed only in some patients. The majority (9 patients) at a certain stage required total arthroplasty (prosthetics) of one or both hip joints; however, in 4 patients conservative therapy led to stabilization of the process in one or both joints. As a result, at the moment, the surgery is delayed. In total, from among the 24 affected joints, the following data have been obtained, namely:

6 – positive dynamics;
3 – negative or no dynamics;
4 – hip arthroplasty is indicated, but not performed yet;
9 – hip arthroplasty has been performed;
2 – no data.

The practicing rheumatologist should always be alert to possible side effects of glucocorticoids and monitor the patient's health parameters for its early detection. ANFH is one of the most serious complications and requires special caution. Therefore, it is recommended to perform X-ray radiography and, if necessary, MRI of the hip joints in all patients with SLE with pain in one or both hip joints, which will make it possible to identify this condition at the earliest possible stage [15].

Along with this, the more important task is to prevent the development of ANFH by identifying and monitoring risk factors. In particular, our research has revealed that patients with ANFH had significantly higher levels of uric acid and total cholesterol in the blood serum, as well as a total dose of GCs compared with the control group. The study conducted involving larger number of patients also showed a difference in other parameters. In particular, it has been revealed that patients with ANFH have lower levels of hemoglobin, glucose, vitamins B6 and B12, as well as higher levels of creatinine, sodium and homocysteine [5]. These facts require further study, but suggest the need for targeted monitoring of these parameters in patients with SLE.

Regarding the level of uric acid, there is contradictory information on its association with development of ANFH. A possible mechanism is the ability of uric acid to increase spontaneous and ADP-induced platelet aggregation. It has also been proven that in patients suffering from SLE, high levels of uric acid are associated with hyperlipidemia and the presence of arterial thrombosis, which are independent risk factors for the development of ANFH [5, 11, 12].

A recent retrospective study has revealed that increased levels of low-density lipoprotein are associated with an increased risk of ANFH occurrence. Fat embolism and hypertrophy of adipocytes of the yellow bone marrow are considered among the possible pathogenic mechanisms, leading to extravasal compression of the vessels of the microvasculature [10]. In the course of our research, we have obtained similar data by comparing total cholesterol levels. Statins have been shown to reduce the risk of ANFH in many animal models and several patient studies. [4, 14]. Therefore, the use of lipid-lowering agents can be considered as one of the possible ways to prevent the development of ANFH in high-risk patients.

Along with this, there are also data on the protective effect of administering vasodilators, antiplatelets and anticoagulants [3], which is consistent with our data obtained concerning the more frequent development of ANFH in patients with vascular pathology.

The fact of earlier occurrence of ANFH in patients with later SLE onset deserves special attention. Two important conclusions can be drawn from this predicted pattern, as follows:

– young patients have a time interval during which achievement of remission (without glucocorticoids or at their minimum doses) will minimize the risk of ANFH development;

– in older patients doctors should be more vigilant against ANFH in the early years of the disease and may consider earlier use of bisphosphonates, vasodilators, statins, or intensification of cytostatic therapy in order to minimize glucocorticoid doses.

Possible reasons for this predicted pattern that require further research are a decrease in bone mineral density and an progression of degenerative changes in the joints with age.

Conservative therapy used for treating our patients gave a certain positive effect only in 4 cases (6 joints), while in the majority of the patients total hip arthroplasty of 1 or 2 joints was needed. However, even such results make it possible to rely on pharmacotherapeutic approaches as a way to stop the development of ANFH and improve the patient's condition, especially in early diagnosis and in combination with non-radical surgical techniques. The latter have gained widespread use and include the technique of vascularized or non-vascularized fibular transplant, decompression, stem cell transplantation, osteotomy and others.

Conclusions

1. Avascular necrosis of the femoral head occurred in 8.7 % of patients. It has been revealed that with the increase in the age of SLE onset, the risk of this complication in the first years of the disease increases, which requires higher alertness of doctors.

2. The level of cholesterol, uric acid in the serum, as well as the total dose of glucocorticoids are significantly higher in patients with ANFH compared with the control group by 1.2, 1.26 and 1.86 times, respectively. From among the clinical manifestations, the presence of vascular pathology, alopecia and lymphopenia is associated with an increased risk of ANFH development (RR is 2.4 (1.16–3.64); 3.03 (1.71–4.35) and 3.28 (1.59–4.97) respectively).

3. Most patients with ANFH require hip replacement surgery; however, conservative treatment with bisphosphonates, vasodilators, antiplatelet agents, and lipid-lowering drugs can slow down disease progression in some cases.

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