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PROGNOSIS OF NEUROLOGICAL DISORDERS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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The study was devoted to the problem of predicting neurological disorders occurring in patients with systemic lupus erythematosus. Various clinical and paraclinical parameters, such as disease activity, clinical manifestations of the disease, the presence of certain types of antibodies, and so on, have been proposed as possible predictors of the development of neurological disorders in this disease. We performed a comprehensive examination of 64 patients with systemic lupus erythematosus. Based on the obtained results of clinical-neurological, neuropsychological, neuroimaging and immunological studies, we identified the main factors that can be considered predictors of the development of neurological manifestations of systemic lupus erythematosus, the most significant role among which is assigned to antiphospholipid antibodies. Using the obtained data, a predictive model of neurological disorders in patients with lupus was subsequently developed.

Key words: neuropsychiatric systemic lupus erythematosus, autoantibodies, antiphospholipid antibodies, prognosis, predictors.

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ПРОГНОЗУВАННЯ НЕВРОЛОГІЧНИХ РОЗЛАДІВ У ХВОРИХ НА СИСТЕМНИЙ ЧЕРВОНИЙ ВОВЧАК

Стаття присвячена проблемі прогнозування неврологічних порушень, що виникають у пацієнтів із системним червоним вовчаком. Як можливі предиктори розвитку неврологічних розладів при цьому захворюванні були запропоновані різні клінічні та параклінічні параметри, такі як активність захворювання, клінічні прояви захворювання, наявність певних видів антитіл і так далі. Нами було проведено комплексне обстеження 64 пацієнтів із системним червоним вовчаком. На підставі отриманих результатів клініко-неврологічного, нейропсихологічного, нейровізуалізаційного та імунологічного досліджень нами були виділені основні фактори, які можуть розглядатися як предиктори розвитку неврологічних проявів системного червоного вовчака, найбільша роль серед яких відводиться антифосфоліпідним антитілам. Використовуючи отримані дані, згодом була розроблена прогностична модель неврологічних порушень у пацієнтів з вовчаком.

Ключові слова: нейропсихіатричний системний червоний вовчак, автоантитіла, антифосфоліпідні антитіла, прогнозування, предиктори.

The study is a fragment of the research project "Clinical, pathogenetic and prognostic markers of disorders of the nervous system and optimization of diagnostic and treatment algorithms", state registration No. 0122U201970.

Systemic lupus erythematosus (SLE) is a multiple autoimmune syndrome characterized by multiple lesions of many organs and systems that arise as a result of the action of autoantibodies and, as a result, is characterized by a wide variety of clinical manifestations [1, 7].

A typical manifestation of SLE is the development of neurological and psychiatric symptoms, which in foreign literature and the medical practice of these countries is called "neuropsychiatric SLE" (NPSLE). Data on its prevalence vary greatly depending on whether so-called "minor signs" such as mild depression or anxiety and other features of the study design are taken into account, ranging from 6 to 91 % [13], and in the early stages of SLE, neurological disorders are registered in 39–50 % of cases [8].

It has been established that neurological symptoms can appear both at an advanced stage of the development of SLE during its activity, or they can be the first or only manifestation of the disease. A comprehensive assessment of clinical, laboratory and neuroimaging data is necessary to establish whether these or other symptoms are a manifestation of NPSLE or another disease [15].

Research data indicate that NPSLE is associated with a high frequency of hospitalizations, a high level of patient disability and a higher mortality rate [2], which leads to an increase in direct and indirect costs and, as a result, significant social and economic losses. In addition, it is known that neurological disorders have a significant negative impact on the quality of life of patients with lupus [12]. That is why the prediction of neurological disorders of SLE is a highly relevant issue, the solution of which is currently devoted to many global studies.

Several factors are considered predictors of neurological disorders in patients with SLE. So, for example, some researchers estimate the specificity and sensitivity of clinical and neurological manifestations of lupus at 37.1 % and 97.4 %, respectively, with a positive predictive value of 70 %, and the sensitivity and specificity of positive results of tests for the presence of antibodies are 84 % and 53 %, respectively, with a predictive value of a positive outcome of 71.1 %.

In addition, the disease activity index is considered a possible predictor of neurological disorders [5].

Much attention in this issue is paid to autoantibodies in the blood and cerebrospinal fluid of patients with SLE. So, for example, numerous data have been found regarding the connection of neuropsychiatric manifestations of SLE with anti-ribosomal antibodies, anti-Sm antibodies, antinuclear antibodies (ANA) and antiphospholipid antibodies, first of all – lupus anticoagulant (LA) and anticardiolipin (ACL) antibodies. [4, 6, 10].

Neuroimaging examination, first of all – magnetic resonance imaging (MRI), is one of the critical studies in NPSLE. In patients with neurological disorders in SLE, several pathological changes in the brain were described during this study, the main of which are cerebral atrophy, demyelinating disease, ischemic, hemorrhagic and inflammatory changes, but they were registered in 20–70 % of patients with SLE [14], however, their prognostic and diagnostic role is questionable.

Thus, a wide range of factors are currently being considered for the role of prognostic factors in the occurrence of neurological symptoms in SLE. Still, a single predictive model has not been developed to date.

The purpose of the study was to develop a predictive model for the occurrence of neurological disorders in patients with systemic lupus erythematosus.

Material and methods. We examined 64 patients with SLE who underwent inpatient treatment in the Rheumatology Department of the Communal Institution "Dnipropetrovsk Regional Clinical Hospital, named after I.I. Mechnykov" of DRC" from 2018 to 2021. Before starting all research procedures, all patients signed informed consent to participate in the study. All study participants were divided into 2 groups – group 1 (baseline) and group 2 (comparison) – based on the presence or absence of neurological symptoms. All patients underwent in-depth clinical, neurological, psychodiagnostic assessment, neuroimaging, and laboratory research. Neuropsychological testing included assessment of cognitive abilities using the Montreal Cognitive Assessment (MoCA), assessment of psychoemotional status using the Hospital Anxiety and Depression Scale (HADS) and other psychodiagnostic methods. The neuroimaging examination included an MRI of the brain with calculation of linear morphometric indices of brain atrophy – BFR, BCR, SFR, FFR. The laboratory study included conducting blood tests for the detection of ANA with the determination of their titer, LA with the calculation of the values of the screening (LA1), confirmatory (LA2) tests, as well as their ratio (LA1/LA2) and blood test for the detection of ACL and determination of their titer. Parametric and non-parametric statistics methods were used to process the data. To determine the discriminative ability of parameters, ROC analysis (ROC – Receiver Operating Characteristic curve analysis) was performed. It included construction and analysis of operating characteristic curves, determination of the area under the ROC curve (AUC – Area under the curve) with the standard error of the area under the curve and 95 % confidence interval (95 % CI); indices of sensitivity (Se) and specificity (SP). The value of the area under the curve was interpreted as indicators of diagnostic accuracy: 0.9–1.0 – excellent; 0.8–0.9 – very good; 0.7–0.8 – good; 0.6–0.7 – mean; 0.5–0.6 – unsatisfactory; a value of 0.5 indicates the unsuitability of the method. The critical value of the statistical significance level (p) for all types of analysis was assumed to be <5 % ($p<0.05$). The results of the study were processed using a personal computer using Microsoft Excel software products (Microsoft Office 2016 Professional Plus, Open License 67528927), STATISTICA 6.1 (StatSoftInc., serial number AGAR909E415822FA) and MedCalc Statistical software trial version 20.009 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2021).

Results of the study and their discussion. Considering the large number of connections, intra-group and inter-group, between clinical and immunological parameters and the results of neuropsychological and neuroimaging studies, a canonical correlation analysis was performed for these groups of variables. As a result of the canonical correlation analysis, statistically significant results were obtained regarding the canonical roots in the case of analyzing the relationship between the combined results of neuropsychological and neuroimaging studies and the titer level of the studied antibodies ($p<0.05$), the canonical correlation coefficient was $R=0.70$ ($\chi2=81.95$; $P=0.032$), which allows us to assert the presence of a strong relationship between the studied parameters. The load of canonical factors shows that among the neuropsychological indicators, MoCA (-0.865), atrophy indices FFR (0.859) and BCR (0.827) have the most significant load on the generalized factor of neuroimmunological indices.

ROC analysis was performed to assess the ability of immunological markers to predict neurological manifestations in SLE (Table 1).

ACL titers ($Se=74.07$; $SP=90.0$; $AUC=0.881$; $p<0.001$) and LA1/LA2 index ($Se=61.11$; $SP=100$; $AUC=0.819$; $p<0.001$) had the best operational characteristics (highest sensitivity and specificity, AUC). When comparing these ROC curves, no statistically significant differences were found ($p>0.05$).

Therefore, only the ACL titer and the LA1/LA2 index can predict neurological manifestations in systemic lupus erythematosus. Considering the somewhat low sensitivity level in the ratio LA1/LA2 ($Se=61.11$), it is more appropriate, according to the results of the ROC analysis, to use ACL in practice.

Table 1

Evaluation of predictive capabilities of autoimmune markers in predicting neurological manifestations in systemic lupus erythematosus (operating characteristics according to ROC analysis data)

Markers	AUC	SE AUC	95 % CI AUC	p	Se	Sp	Optimal cut-off point
ACL titer	0.881	0.048	0.775–0.948	<0.001	74.07	90.0	>2.3
ANA titer	0.725	0.096	0.597– 0.831	0.019	90.38	50.0	>0
LA1 time	0.722	0.068	0.596–0.827	0.001	68.52	80.0	>49.1
LA2 time	0.763	0.087	0.640–0.860	0.002	79.63	70.0	≤37.9
LA1/LA2 index	0.819	0.055	0.702–0.904	<0.001	61.11	100	>1.49

Notes. AUC – Area Under Curve; SE – Standard Error; Se – Sensitivity; Sp – Specificity; Optimal cut-off point.

The optimal cut-off points that can be used as a critical level of an immunological marker to decide the prognosis of neurological manifestations in systemic lupus erythematosus are ACL>2.3 and LA1/LA2>1.49.

The threshold value of the optimal cut-off points of the studied parameters was used to calculate the odds ratio (OR) with a 95 % confidence interval (95 % CI) by simple logistic regression analysis.

An odds ratio of 1 means no effect. A value of OR from 0 to 1 corresponds to a reduction in risk. The OR greater than 1 indicates an increased risk. The higher the odds ratio, the stronger the index's impact on the disorder's development.

Therefore, the chances of developing neurological manifestations in systemic lupus erythematosus increase with the titer of the studied ANA, ACL and LA ($p<0.05$). When the LA1/LA2 index value is>1.49, the chances of neurological disorders in patients with SLE increase by 32.72 times (95 % CI 1.82–587.77); with ACL titer>2.3 – by 25.71 times (95 % CI 2.98–221.60); with time of LA2≤37.9 – by 9.12 times (95 % CI 2.02–41.12); with time of LA1>49.1 – 8.71 times (95 % CI 1.67–45.45); when the ANA titer>0 – 6.71 times (95 % CI 1.54–29.26).

To assess the probability of developing neurological disorders in patients with systemic lupus erythematosus, a multiple logistic regression analysis was performed with indicators that can potentially be used as predictors determined by the previous correlation (paired and canonical) and ROC analysis results. A logistic equation was used as a basis, which assumes that an unfavourable outcome (neurological disorders) is associated with factors according to the formula:

$$y=\exp(b0+b1\text{-}n\times X1\text{-}n)/[1+\exp(b0+b1\text{-}n\times X1\text{-}n)],$$

where y is a result (probability of neurological disorders in patients with SLE);

b0 is a coefficient indicating the value of the result in the case when the predictor is equal to 0;

b1-n are regression coefficients showing how much the logarithm of the chance of developing neurological disorders will change on average when the independent variable changes by one unit of its measurement;

x1-n are predictor variables, indicators of each individual patient for whom the prognosis is calculated.

For the determined predictors, the parameter is entered into the equation using the values of the obtained measurement units. Regardless of the values of x, the predicted value of the result (y) in this model will always lie in the range from 0 (absence of neurological disorders) to 1 (development of neurological disorders). According to generally accepted approaches, if the calculated probability is less than 0.5, it can be assumed that the event will not occur (there will be no neurological disorders). If the probability is more significant than 0.5, the development of neurological disorders is predicted.

As a result of the step-by-step inclusion of independent variables, the parameters of the logistic regression equation were obtained (Table 2).

Table 2

Prediction of neurological disorders in patients with SLE based on multiple logistic regression analysis

Predictive variables	Regression coefficient β	Standard error of coefficient β	χ^2 Wald test	p-value χ^2 Wald	Adjusted OR (95 % CI)
Free term of the equation	39.021	-	-	-	-
MoCA (x_1)	-1.486	0.838	3.144	0.018	0.40 (0.18–0.86)
Index of bifrontal ratio (BFR)(x_2)	0.727	0.382	3.621	0.009	1.77 (1.59–2.18)
HADS Test Anxiety (x_3)	-26.250	24.175	1.179	0.006	1.84 (1.19–2.84)
LA1/LA2 index (x_4)	3.150	2.045	2.373	0.020	77.01 (1.98–299.52)

Note. Only statistically significant predictors are included in the table.

Taking into account the obtained data, the equation for predicting neurological disorders in patients with SLE looks like this:

$$y=\exp(39.021-1.486\times x1+0.727\times x2-26.250\times x3+3.150\times x4)/$$
$$[1+\exp(39.021-1.486\times x1+0.727\times x2-26.250\times x3+3.150\times x4)]$$

The predictive accuracy of the logistic regression equation, which was assessed as adequate and statistically significant, was evaluated using the Chi-square value: $\chi 2=40.12$ ($p<0.001$); percentage of concordance – the share of observations correctly reclassified using the equation (93.75 %); the Hosmer-Lemeshov agreement test ($p=0.999$, which allows us to accept the null hypothesis regarding the consistency of the theoretical and actual course of the disease) and ROC analysis.

The logistic regression equation has operational characteristics – sensitivity 92.59 %, specificity 100.00 %, and the area under the ROC curve – 0.981 (95 % CI 0.911–0.999), which characterizes the predictive ability of the obtained regression equation as excellent.

Therefore, the data we obtained regarding the predictors of the development of neurological disorders in SLE generally coincide with the data of global research in this field, although there are specific differences. For example, some researchers attribute a significant role in this issue to factors such as the duration of the disease, its activity, ethnicity, education level, and cardiovascular risk factors [3]. In our study, the above-mentioned factors were not taken into account. Instead, our study focused on the results of immunological, neuropsychological and neuroimaging examinations. Special attention was paid to laboratory markers – antiphospholipid antibodies and ANA. It should be noted that the role of antiphospholipid antibodies, including LA and ACL, in developing neurological manifestations of SLE has long been a subject of study. It is believed that they lead to the emergence of neuropsychiatric symptoms in patients with SLE primarily through the implementation of their procoagulant and prothrombotic properties [11]. Among patients with SLE, the risk of neuropsychiatric symptoms is significantly higher in people who have a positive result for the presence of antiphospholipid antibodies than in those who do not have these antibodies, and their presence is considered a vital risk factor for neurolupus [4]. In particular, they indicate the possible role of these antibodies in the occurrence of such manifestations as stroke, myelopathy, epileptic seizures, movement disorders, and cognitive dysfunction [9].

Therefore, despite the specific results obtained in our study, it should be determined that the problem of predicting neurological disorders in patients with SLE requires further comprehensive study.

Conclusions

1. Neurological disorders are one of the most frequent manifestations of SLE. They are associated with a high level of mortality and disability of patients, as well as with a low level of quality of life.

2. A wide variety of factors are considered as possible prognostic factors for the occurrence of NPSLE – from the peculiarities of the course of the disease and its activity to immunological markers and neuroimaging findings

3. A high titer of ACL predicts the development of neurological disorders in patients with SLE.

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COMPARATIVE MORPHOMETRIC CHARACTERISTICS OF THE RECTUS FEMORIS MUSCLE OF THE HIP ACCORDING TO THE DATA OF THE ULTRASOUND STUDY

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The study was performed on 48 young men aged 16 to 18. The main group consists of 32 respondents, the control group – of 16 students. All respondents underwent a morphometric study using ultrasound diagnostics of the rectus femoris muscle. As a result of the comparison of the morphometric parameters of the bipinnate (rectus) femoris muscle according to the ultrasound examination, it was established that the volume in the upper third of the m.réctus fémoris is greater in professional football players, compared to student football players, by 31.2 %, by 37.6 %, compared to the control group. Also, in football students the volume of m.réctus fémoris in the upper third is by 9.4 % larger, compared to the control group. In the middle third, it is higher in professional football players by 39.3 % compared to student football players and by 35.4 % compared to the control group. In the lower third, it is higher in professional football players by 28.1 %, compared to student football players, and by 21.1 %, compared to the control group. There is practically no difference in the volume of the m.réctus fémoris in the middle and lower third between football students and the control group.

Key words: muscles, anatomy, morphometry, ultrasound examination.

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ПОРІВНЯЛЬНА МОРФОМЕТРИЧНА ХАРАКТЕРИСТИКА ДВОПЕРИСТОГО М'ЯЗА СТЕГНА ЗА ДАНИМИ УЛЬТРАЗВУКОВОГО ДОСЛІДЖЕННЯ

Дослідження виконано на 48-ми юнаках, віком від 16 до 18 років, Основну групу становлять 32 респондента, контрольну – 16 студентів Усім респондентам було проведено морфометричне дослідження за допомогою ультразвукової діагностики прямого м'яза стегна. В результаті проведеного порівняння морфометричних параметрів двоперистого (прямого) м'яза стегна за даними ультразвукового дослідження встановлено, що об'єм у верхній третині m.réctus fémoris більший у професійних футболістів, порівняно з студентами-футболістами на 31,2 %, на 37,6 %, порівняно з контрольною групою. Також, у студентів-футболістів об'єм m.réctus fémoris в верхній третині на 9,4 % більший, порівняно з контрольною групою. В середній третині більший у професійних футболістів на 39,3 %, порівняно з студентами-футболістами та на 35,4 %, порівняно з контрольною групою. В нижній третині більший у професійних футболістів на 28,1 %, порівняно з студентами-футболістами, та на 21,1 %, порівняно з контрольною групою. Різниці об'єму m.réctus fémoris в середній та нижній третині між студентами-футболістами та контрольною групою практично немає.

Ключові слова: м'язи, анатомія, морфометрія, ультразвукове дослідження.

The work is a fragment of the research project "Regularities of sex-age structure and topographic-anatomical transformations of organs and structures of the body at the pre- and postnatal stages of ontogenesis. Peculiarities of perinatal anatomy and embryotopography", state registration No. 0120U101571.

Individual features of the athletes' body structure have a significant impact on the parameters of the coordination structure and are an objective cause of the variability of the movement system, which should be taken into account when correcting the individual model of the athletes' movement structure [1-5]. But in order to achieve certain success in sports, in addition to the study of biometric, anthropometric indices and the establishment of biomechanical technologies, morphometry is important for planning promising sports achievements. It should be noted that in the field of sports, information about muscle morphology is very valuable for diagnosis or further research after treatment or training [12].