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CLINICAL AND DIAGNOSTIC PARALLELS IN POST-STROKE EPILEPSY, POSSIBILITIES OF THERAPEUTIC TACTICS

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ABSTRACT

It is known that stroke and epilepsy have a two-way connection: not only is stroke an etiological factor of epilepsy, but also the first epileptic seizures in old age increase the risk of stroke. As with many other neurological diseases, research is actively conducted to find biomarkers of possible development of epilepsy after a stroke. Effective approaches to drug therapy for patients with post-stroke epilepsy are being developed.

Key words: Post-stroke epilepsy (PSE), clinical scales, neuron-specific enolase (NSE), blood serum.

INTRODUCTION

It is known that stroke and epilepsy have a two-way connection: not only is stroke an etiological factor of epilepsy, but also the first epileptic seizures in old age increase the risk of stroke threefold. As with many other neurological diseases, research is actively conducted to find biomarkers of possible development of epilepsy after a stroke. Effective approaches to drug therapy for patients with post-stroke epilepsy are being developed.

Various biomarkers can act as predictors of epileptogenesis after stroke. A biomarker can be considered an objectively measurable characteristic of a normal or pathological biological process. Acute neuronal damage induced by stroke triggers a neuroinflammatory cascade, which releases various inflammatory

mediators, i.e. damage-associated molecular patterns (DAMPs), cytokines, prostaglandins, chemokines, complement, growth factors, etc.

An increase or decrease in the concentration of various biomarkers can serve as an indicator of the presence or progression of a disease [1], and some of them have a neuroprotective effect [2], which serves as the basis for their study.

THE AIM OF THE STUDY

To study the indices of neuron-specific enolase (NSE) in patients with post-stroke epilepsy (PSE) and stroke and their relationship with the indicators of the neurological scales NIHSS, Rankin, Barthel and SeLECT with the study of clinical and neuroimmunological correlations.

MATERIAL AND METHODS OF RESEARCH

140 patients aged 28 to 84 years with consequences of the first ischemic stroke were examined. Of these, 70 patients developed late epileptic seizures for the first time (main group), 70 had ischemic stroke without epileptic seizures (comparison group), The control group included 30 patients without ischemic stroke and epilepsy.The severity of ischemic stroke was assessed using the National Stroke Scale institutes National Institutes of Health Stroke Scale (NIHSS), the degree of disability - according to the modified Rankin Scale (mRS), the level of basic functional activity of the patient - according to the Barthel scale. Prediction of the occurrence of late attacks after ischemic stroke was carried out using the SeLECT scale (SEverity of stroke, large artery atherosclerosis, early seizure, cortical involvement, territory of the middle cerebral artery). The level of neuron-specific enolase (NSE) in the blood serum of patients was studied in all patients using solid-phase ELISA analysis.

Depending on the therapy received, patients with PIE (n = 70) were divided into 2 treatment subgroups:

Group 1a (comparison treatment group) – 35 patients with PIE who received traditional combination therapy for the treatment of IS and additionally AET for the treatment of epileptic seizures in the form of monotherapy with one of the first-choice AET for this form of epilepsy (starting or subsequent, including after inadequate polytherapy) ;

Group 1b (main treatment group) – 35 patients with PIE, who, as part of traditional complex therapy for IS, additionally took antiepileptic drugs against epileptic seizures and a neuroprotector with antioxidant properties, edaravone, in the form of an injection solution of 1.5 mg/ml, 20 ml in 100.0 ml. isotonic sodium chloride solution intravenously by drip over 30 minutes every 12-24 hours for 10 days according to the regimen we developed.

RESULTS AND DISCUSSION

At the time of admission of patients to the hospital, a significant increase in the NSE level in the blood serum of patients was detected, the indicators of which averaged 18.42 ± 3.0 ng / ml in the main group (n = 70) and 17.34 ± 3.37 ng / ml in the comparison group (n = 70), which was higher than the values of the control group (n = 15) (3.9 ± 1.3 ng / ml) by 4.72 and 4.45 times, respectively (P < 0.001) (Table 4.1). At the same time, the NSE level in group 1 statistically significantly exceeded this indicator in group 2 by 1.06 times (P = 0.04) (Fig. 1).

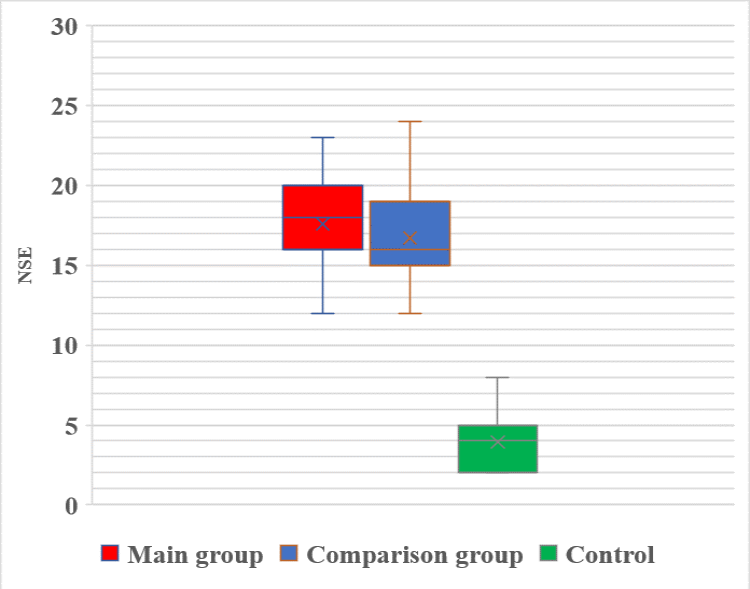


Fig. 1. The level of neuron-specific enolase NSE in the blood serum of examined patients and the control group (ng/ml).

NSE values were observed in patients with moderate and severe IS in both groups. This indicates that this biomarker is an unfavorable prognostic factor for neurological deficit and the development of epilepsy after IS.

As a result of the conducted correlation analysis between the NSE level and the scores on the assessment scales in patients with PIE, a direct strong relationship was found between the NSE level and the scores on the NIHSS scale (r = 0.71) (Fig. 2). This may indicate that an increase in the NSE level is a marker of severe IS and an unfavorable prognosis in patients with PIE. A direct average relationship was determined between the NSE level and the scores on the Rankin scale (r = 0.50) (Fig. 4.2), which may indicate that this marker is interconnected with the degree of disability of patients with PIE and its further growth may negatively affect the rehabilitation period.

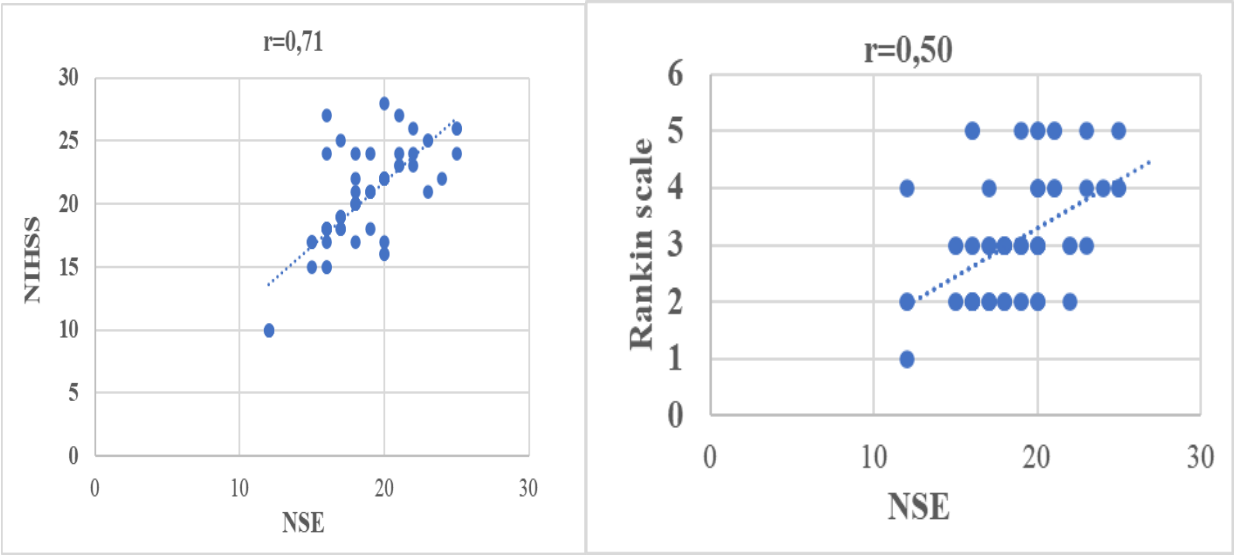


Fig. 2. Correlation relationships (r) between the NSE level, NIHSS and Rankin scale scores in post-stroke epilepsy.

A weak correlation was found between the NSE level and the Barthel scale scores (r = 0.31) (Fig. 3). The Barthel index indicates the patient's activity and dependence in everyday life. Therefore, a high NSE level may indirectly affect the activity of patients with PIE due to the severity of neurological deficit.

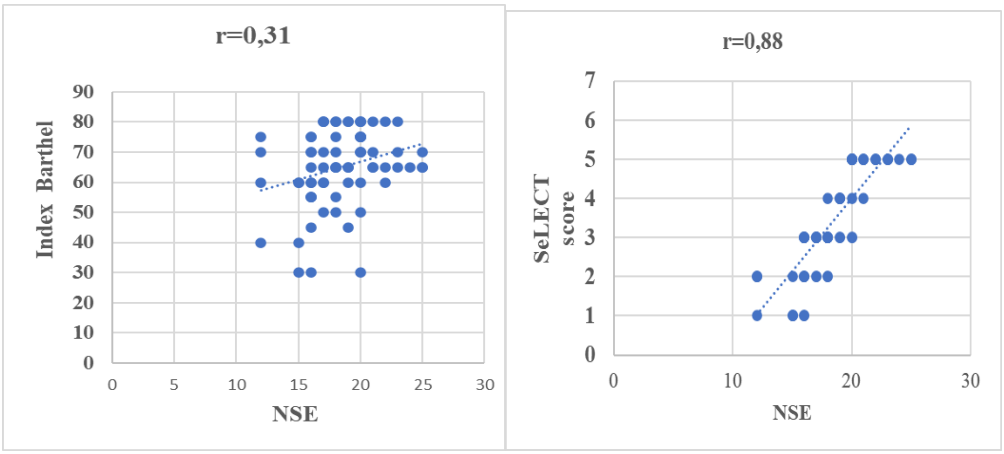


Fig. 3. Correlation relationships (r) between the NSE level, scores on the Barthel and SeLECT scales score in post-stroke epilepsy.

The correlation coefficient between the level of the neurotrophic factor NSE and the scores on the SeLECT scale was r = 0.88, i.e. a direct strong relationship was determined (Fig. 4.3). Taking into account that the scale can predict a 0.7% risk of late seizures within 1 year after stroke, a 1.3% risk within 5 years, while the highest value (9 points) predicts a 63% risk of late seizures within 1 year, 83% within 5 years [3], and also that the higher the scores on the scale, the higher the NSE level and vice versa, we can state the validity of this scale and the studied

biomarker as predictors of the risk of developing late epileptic seizures after stroke. Our results are consistent with the data of other researchers [4].

Thus, in patients with consequences of IS and epileptic seizures, a reliable increase in the concentration of the neurotrophic factor NSE in the blood serum was revealed by 1.06 times compared to patients with IS without epilepsy and by 4.72 times relative to the control group, which indicates a more significant destruction of nerve tissue in patients with PIE. Consequently, the use of NSE as a marker of brain damage can improve the accuracy of diagnosis and prognosis of the outcome of PIE.

The principles of AED selection depended on such factors as seizure type, epileptic syndrome, age and gender of the patient, efficacy and side effects of the respective drug, as well as drug interactions. According to the ILAE recommendations, in the treatment PIE It is mandatory to prescribe AEP, which is used when early attacks appear for a short time (with subsequent reassessment of the risks of discontinuing therapy) and for a long time for late attacks, which can currently be considered the debut of PIE [5]. It is advisable to give preference to new generation drugs - lamotrigine and levetiracetam [6].

The effectiveness of therapy was assessed according to standard criteria for the reduction in the frequency of epileptic seizures as a percentage of the initial frequency and the restoration of neurological deficit as follows:

- 100% disappearance of seizures (remission) and improvement of neurological status for 12 months or more;
- 75-99% – significant improvement;
- 50-74% – moderate improvement;
- a reduction in seizure frequency of less than 50% is a minimal improvement that was considered to have no clinically significant effect;
- increased frequency of attacks – deterioration.

In both treatment groups, especially in the group receiving edaravone, a more pronounced recovery in the sphere of complex functions of the higher nervous activity was noted, a general increase in mental activity was revealed, mood and memory improved, speech disorders were restored, motivation for recovery and further rehabilitation appeared. In all groups, complaints about epileptic seizures decreased, especially against the background of edaravone, which may be associated with the prescription of AEDs and additional antioxidant neuroprotective therapy.

The safety and tolerability of treatment were assessed by the presence or absence of adverse reactions.

The efficacy of edaravone was evaluated according to the patients' clinical symptoms and manifestations of PIE and their stroke scale scores. The NIHSS scale was used to evaluate the patients' neurological impairment before treatment and after therapy at the first and second weeks of treatment. A high NIHSS score implied severe neurological impairment. Recovery criteria: the clinical symptoms disappeared, the NIHSS score decreased from 91% to 100%, and the disability degree according to the Rankin Scale decreased to grade 0; excellent efficacy: the clinical symptoms clearly improved, the NIHSS score decreased from 46% to 90%, and the disability degree decreased to grades 1-3; partially effective treatment: the clinical symptoms slightly decreased, the NIHSS score decreased from 18% to 45%, and the patients basically regained the ability to take care of themselves in daily life; ineffective treatment: clinical symptoms did not improve, even worsened, and the NIHSS score was reduced to a level of no more than 17%. The overall treatment effectiveness was calculated as follows: edaravone effectiveness = recovery percentage + maximum effectiveness + partial effectiveness.

According to our data, the NIHSS score showed a decrease in scores by 49.81% and 38.65%, respectively, in the main and compared treatment groups ($P < 0.05$). The Rankin scale scores also tended to decrease by 23.7% and 4.9%, respectively, in the treatment groups (Table 4.). That is, against the background of treatment with edaravone as part of complex therapy, a noticeable improvement in clinical symptoms and a decrease in the degree of disability with restoration of the ability to self-care were noted, and against the background of traditional therapy, clinical symptoms decreased partially and in many cases the degree of disability remained the same.

After 10-14 days, the Barthel Activities of Daily Living Scale was used to assess the patients' baseline functional activity and quality of life. A high score corresponded to an improvement in the disease outcome and quality of life of the patients (Table 1).

Table 1

Comparative characteristics of neurological disorders and functional activity according to scales in the dynamics of treatment in the compared treatment groups (points)

Scales	Main treatment group (n=35)		Comparison treatment group (n=35)	
	Before treatment	After treatment	Before treatment	After treatment
NIHSS	15.54±2.9	7.8±0.44* ^	15.81±0.95	9.7±1.34** ^
Rankin mRS	3.8±0.43	2.9±0.6*	4.1±0.6	3.9±1.5 ^
Barthel Index	65.1±4.5	88.7±2.8	65.6±2.9	80.2±1.3** ^
SeLECT score	2.94±0.43	1.8±0.12	3.41±0.84	2.5±0.52** ^

Note: * – reliability of differences before and after therapy - $P< 0.001$; ** – reliability of differences before and after therapy $P<0.05$; ^ – reliability of differences between the main group and the comparison group.

Due to the decrease in scores on the NIHSS stroke severity scale, scores on the SeLECT score scale for predicting late seizures after ischemic stroke decreased accordingly (Table 4.2), which may indicate a decrease in the risk of epileptic seizures within 1 year to 5 years (risk from 0.7% to 3%) [7].

Despite the disparity in the increase in scores on the severity scales of IS, as well as the degree of disability on the Rankin scale and the outcome of IS on the Barthel index, depending on the presence of epilepsy, the inclusion of edaravone in the complex rehabilitation therapy of PIE turned out to be the most effective.

Thus, analysis of data obtained using the assessment scales during treatment clearly demonstrated that by the end of treatment, the average increase in scores on each scale was higher after treatment, especially when edaravone was used as part of traditional therapy with the inclusion of AEDs.

In order to evaluate the effectiveness of therapy for epileptic seizures, we conducted EEG studies in all patients with PIE. In 95.4% of patients after treatment on days 10-14, the EEG and/or video-EEG monitoring method allowed us to determine the specificity of the effect of traditional therapy with the inclusion of AED monotherapy, as well as combined use with edaravone, on the bioelectrical activity of the brain of patients. The analysis of the relative value of the power of the rhythms of the brain of patients by the EEG method showed that the restoration of normal values of EEG rhythms against the background of a combination of traditional treatment with AET and edaravone occurs faster than with traditional treatment and AED monotherapy, which did not lead to complete remission of the epileptic syndrome in most patients during treatment for 10-14 days.

Thus, against the background of treatment with edaravone as part of complex therapy for PIE, a significant improvement in clinical symptoms and a decrease in the degree of disability with restoration of the ability to self-care, as well as an improvement in the outcome of the disease and the quality of life of patients were noted. When assessing the EEG in dynamics, it could be noted that, despite the achievement of drug remission in a number of observations, especially against the background of a combination of traditional treatment with AET and edaravone, there was no "normalization" of the EEG in any case. Some decrease in the amplitude of background activity, a decrease in the frequency and severity of paroxysmal manifestations were noted.

In order to objectify the effectiveness of therapy for PIE, immunological studies were conducted in both compared treatment groups of the study before and after therapy.

As can be seen from Table 2, in 70 patients with consequences of ischemic stroke and late epileptic seizures, a reliable increase in the NSE level was observed

both in the main treatment group (n=35) by 4.31 times and in the comparison treatment group (n=35) by 4.75 times compared to the control group (16.81±0.95 and 18.54±2.9 ng/ml versus 3.9±1.3 ng/ml, respectively). (Figures 6 and 7)

Table 2

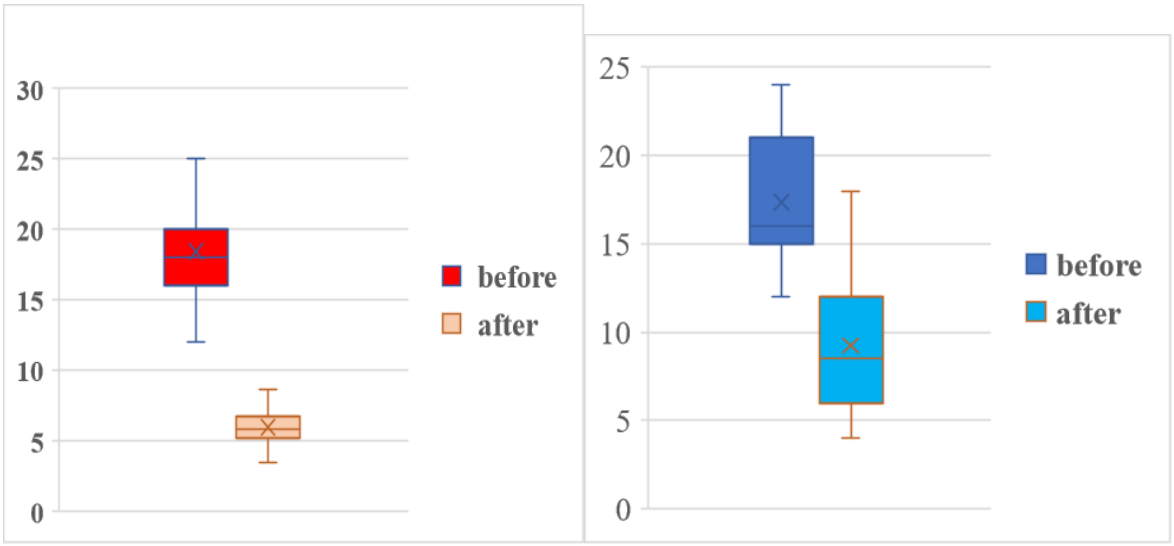
NSE levels in the blood serum of patients with post-stroke epilepsy during treatment.

Indicators	Main treatment group (n=35)		Comparison treatment group (n=35)		Control (n=30)
	Before	After	Before	After	
NSE, ng/ml	16.81±0.95	5.7±1.34** ^	18.54±2.9	8.7±0.44* ^	3.9±1.3

Note: * – reliability of differences before and after therapy P<0.001, **- reliability of differences before and after therapy P<0.05 ^ - reliability of differences between the main group and the control group; # - P<0.001 reliability of differences between the control group.

An increase in neurospecific enzymes and their isoenzymes, in particular NSE, indicates the death of neurons in various lesions of the nervous system, such as epilepsy, Parkinson's disease, senile dementia, Alzheimer's disease, etc. [8]. Determining the level of NSE in the blood serum allows us to objectively judge the depth and intensity of damage to the nervous system. [7]

Figure 6 Figure 7



Main treatment group *Comparison treatment group*

Fig. 6 and 7 NSE levels in compared treatment groups of patients with post-stroke epilepsy before and after therapy (ng/ml).

The inclusion of edaravone in the complex of therapeutic measures of PIE had a beneficial effect on a reliable decrease in the increased expression of NSE by 2.95 times relative to the initial parameters before treatment, amounting to

5.7±1.34 ng/ml, respectively (P< 0.05). However, the studied NSE indices after treatment did not reach the values of the control group, remaining higher than the control values only by 1.46 times, respectively (P< 0.05).

CONCLUSION

1. Determination of the level of neuron-specific enolase in the blood serum of patients with acute ischemic stroke and post-stroke epilepsy revealed a significant increase in its content, which turned out to be higher than the values of the control group (n=15) (3.9±1.3 ng/ml), respectively, by 4.72 and 4.45 times (P<0.001). Hyperexpression of NSE is important in predicting the development or progression (worsening) of epilepsy after ischemic stroke.

2. Correlation analysis between the NSE level in patients with PIE and scores on the assessment scales revealed a direct strong relationship between the NSE level and scores on the NIHSS scale (r = 0.71), which may indicate that an increase in the NSE level is a marker of severe ischemic stroke and an unfavorable prognosis in patients with PIE. A direct average correlation was determined between the NSE level and scores on the Rankin scale (r = 0.50), which indicates that this marker is interconnected with the degree of disability of patients with PIE and its further growth can negatively affect the rehabilitation period.

3. As a result of the complex therapy with the inclusion of edaravone, the overwhelming majority of patients (94.5%) in the main treatment group showed a positive effect. Partial regression of movement disorders, decreased dizziness, improved memory. Positive dynamics were recorded, as a rule, in the case of mild and moderate focal neurological deficit. Coordination disorders, as well as frequency of epileptic seizures.

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