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Dynamics of brain derived neurotrophic factor when using neuromodulation as part of comprehensive rehabilitation after a stroke

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Abstract

The aim of the study was to assess the dynamics of brain derived neurotrophic factor when using neuromodulation.

Material and methods. The study was conducted on the basis of clinical departments of the Medical Institute of the Petro Mohyla Black Sea National University. 140 patients with ischemic stroke were treated. The total sample was randomly divided into 4 clinical groups. Patients in group I (n=30) received standard therapy, which included antithrombotic therapy, antihypertensive drugs, statins, and, according to indications, NSAIDs, antiemetics, insulin and other hypoglycemic drugs, antidepressants, etc. Patients in group II (n=40) received peptidergic compounds (cerebrolysin 40 ml per day) in the acute and long-term periods (a month after discharge). Patients in group III (n=40) received traditional therapy with transcranial micropolarization of the brain. In patients of group IV (n=30) it was used combined neuroprotection in the acute and long-term periods (peptidergic compounds in combination with brain micropolarization).

The level of Brain-Derived Neurotrophic Factor (BDNF) was determined using the enzyme-linked immunosorbent assay (Sigma-Aldrich kit RAB0026, USA) during hospitalization and after 3, 6 and 12 months.

The study was performed in compliance with modern bioethical requirements. All patients signed an informed consent to participate in the study. Statistical analysis performed using analysis of variance using the software Statistica 14.1.25 (TIBCO, USA).
Patients with ischemic stroke were characterized by a decrease in serum BDNF concentration to 10.1±0.3 ng/ml. In all clinical groups, the indicator increased later, with the most pronounced dynamics observed in patients of group IV.
In group I the increment was +44.6%, in group II - +68.3%, in group III - +56.4%, and in group IV - +79.2% with maximum approximation to the reference values.
Conclusions: 1. The use of neuromodulation has a positive effect on the synthesis of neurotrophins. 2. The positive effect of neuromodulation is long-lasting.
Key words: stroke; brain derived neurotrophic factor; neuromodulation; comprehensive rehabilitation

Cerebrovascular pathology occupies one of the leading places in the structure of mortality and causes of disability [1, 2]. According to WHO experts, in 2030 DALY due to stroke and its consequences will increase to 60864 per year, which will be 3.99% of the total number of lost years of healthy life [3]. In economically developed countries, the average age of ischemic stroke is 73 years, and the probability of cerebrovascular disease is 1.6‰ [1, 4].
In those patients who have survived a stroke, self-care capabilities are often limited, social activity decreases [3, 5]. In addition, a previous stroke increases the risk of recurrent stroke by 10% during the first year after discharge, and by 5% each subsequent year. In this regard, the requirements for the treatment and rehabilitation process at the late stages after a previous stroke increase [6, 7].
Currently, only a few therapeutic strategies can be considered the gold standard in the treatment of ischemic stroke [8, 9]. These include the treatment of patients in specialized stroke centers, mechanical or drug recanalization of the main vessels by thrombolysis or endovascular thrombectomy, which allows achieving a reperfusion effect in the first hours after the onset of the disease, as well as the appointment of anticoagulants and antiplatelet agents [8]. The use of neuroprotective drugs, including peptidergic drugs, which have shown very promising results at the stage of experimental studies, has so far demonstrated only a limited effect in clinical practice [10]. The problem of using physical neuromodulation methods, in particular micropolarization and transcranial magnetic stimulation, in neurorehabilitation after ischemic stroke remains unresolved [11-13].

The aim of the study was to assess the dynamics of brain derived neurotrophic factor when using neuromodulation.

Material and methods. The study was conducted on the basis of clinical departments of the Medical Institute of the Petro Mohyla Black Sea National University. 140 patients with ischemic stroke were treated. The total sample was randomly divided into 4 clinical groups. Patients in group I (n=30) received standard therapy, which included antithrombotic therapy, antihypertensive drugs, statins, and, according to indications, NSAIDs, antiemetics, insulin and other hypoglycemic drugs, antidepressants, etc. Patients in group II (n=40) received peptidergic compounds (cerebrolysin 40 ml per day) in the acute and long-term periods (a month after discharge). Patients in group III (n=40) received traditional therapy with transcranial micropolarization of the brain as described by Lefaucheur J.-P. et al. (2017) [14]. Anodal stimulation was used (A-tDCS 1 mA; B: S-tDCS; 20 minutes per procedure), technical support – device "Polaris-Reamed" (Russia). In patients of group IV (n=30) it was used combined neuroprotection in the acute and long-term periods (peptidergic compounds in combination with brain micropolarization).

Inclusion criteria: II degree of moderate severity (NIHSS 5-15 points), consent to participate in the study. Exclusion criteria: severe general condition of the patient, multiple organ failure, concomitant malignant neoplasms, convulsive syndrome of any origin, refusal to participate in the study.

The level of Brain-Derived Neurotrophic Factor (BDNF) was determined using the enzyme-linked immunosorbent assay (Sigma-Aldrich kit RAB0026, USA) [15] during hospitalization and after 3, 6 and 12 months.

The study was performed in compliance with modern bioethical requirements. All patients signed an informed consent to participate in the study [16]. Statistical analysis performed using analysis of variance using the software Statistica 14.1.25 (TIBCO, USA) [17].

Results. Patients with ischemic stroke were characterized by a decrease in serum BDNF concentration to 10.1±0.3 ng/ml. In all clinical groups, the indicator increased later, with the most pronounced dynamics observed in patients of group IV (Table 1).

If 3 months after discharge, the content of neurotrophic factor in group I was 13.5±0.5 ng/ml, then after 6 months it was 14.2±0.4 ng/ml, and after 12 months - 14.6±0.5 ng/ml ($p<0.05$). In group II, the content of BDNF increased from 15.8±0.6 ng/ml to 16.5±0.5 ng/ml after 6 months and to 17.0±0.5 ng/ml after 12 months. A somewhat smaller increase was demonstrated by the indicator in group III - compared to the level determined 3 months after discharge (14.9±0.5 ng/ml), it increased after 6 months to 15.4±0.4 ng/ml, and after 12 months to 15.8±0.4 ng/ml,

which is somewhat inferior to the results obtained in group II, but is a better result than the levels achieved in group I.

Table 1 BDNF content at the remote stage of observation (ng/ml)

Groups	In 3 months	In 6 months	In 12 months
I (n=30)	13.5±0.5	14.2±0.4	14.6±0.5
II (n=40)	15.8±0.6	16.5±0.5	17.0±0.5
III (n=40)	14.9±0.5	15.4±0.4	15.8±0.4
IV (n=30)	16.6±0.4*	17.8±0.6*	18.1±0.5*

Note: * - differences are statistically significant ($p<0.05$)

Finally, in group IV, when using complex multimodal influence, the levels determined were 17.8±0.6 ng/ml after 6 months and 18.1±0.5 ng/ml after 12 months, which is significantly higher than in other clinical groups ($p<0.05$), and exceeds the indicator obtained after 3 months (16.6±0.4 ng/ml) by +9.0%. From the above it is clear that positive changes in the production of neurotrophic factors occur in all clinical groups, but multimodal influence increases the initial values by 1.5-1.8 times, while traditional approaches - only by 1.2 times. Such encouraging results gave rise to hope that it is the content of neurotrophic factor that is an important predictor of better functional recovery at a distant stage after a stroke.

Thus, an increase in the content of BDNF in the blood serum occurred in all clinical groups. At the same time, in group I the increment was +44.6%, in group II - +68.3%, in group III - +56.4%, and in group IV - +79.2% with maximum approximation to the reference values. This indicates the continuation of reparative processes even a year after discharge and the long-term neuromodulatory effect experienced by the patients.

Conclusions:

1. The use of neuromodulation has a positive effect on the synthesis of neurotrophins
2. The positive effect of neuromodulation is long-lasting

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