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COGNITIVE IMPAIRMENT RESTORATION IN PATIENTS SUFFERED WITH STROKE DURING THE POST-COVID PERIOD

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Abstract

Frequency of vascular complications, including strokes, in patients suffered from COVID-19 infection is known to be increased up to 8 times, especially compared with influenza. The purpose: to investigate the fundamental mechanisms of brain ischemia in the patients with mnestic dysfunctions who previously underwent COVID-19 through pharmacocorrection via Phenibut (γ -amino- β -phenylbutyric acid hydrochloride) and magnetic therapy in the early recovery period of ischemic stroke. The authors describe the possibilities of cognitive rehabilitation for people who have had ischemic stroke in the post-COVID period. Considering that the presence of mnestic dysfunctions has a negative impact on the process of rehabilitation of cerebral accidents, the fundamental mechanisms of brain ischemia in patients with mnestic dysfunctions in the early recovery period in patients who have undergone COVID-19 have been studied through pharmacocorrection via Phenibut (γ -amino- β -phenylbutyric acid hydrochloride) and magnetic therapy. 46 patients aged 40 to 60 years were examined. A comparative study of three randomized clinical groups of patients with

separate and complex use of Phenibut and magnetic stimulation. The effectiveness of the proposed therapy in restoring executive functions was established on the basis of indicators of the MMSE scale, the test for the study of frontal dysfunction – FAB, regression of depressive symptoms and is characterized by a decrease in the score on the GDS scale. The authors conclude that mnemonic disorders are a functional "target" in cerebral ischemia in the post-COVID period, which requires close attention in relation to pharmacocorrection methods and comprehensive rehabilitation and further research, including the elucidate the pathogenetic mechanisms of cerebral ischemia.

Key words: stroke; mnemonic dysfunctions; pathogenetic mechanisms of cerebral ischemia; post-COVID period; pharmacological correction; magnetic therapy

Introduction. It is known that the frequency of vascular complications, including strokes, in patients suffered from COVID-19 infection increases up to 8 times, especially compared with influenza [11, 15, 16]. There is a significant “rejuvenation” of the contingent of stroke survivors against the background of COVID-19 [13]. More often, occlusion of larger vessels is registered, and risk factors for stroke, typical for this kind of ischemic brain damage, are often not detected, especially in case of “young” ischemic stroke (IS), which complicates the usual therapy and rehabilitation [8, 10, 12]. Acute cerebrovascular accident can develop after suffering a COVID-19 infection in the so-called delayed period [10, 15, 18].

The identified clinical manifestations, apparently, are primarily associated with hypercoagulability due to systemic inflammation, cytokine storm, emerging endotheliitis, etc. [19, 21]. An important clinical feature of IS is the frequent development of non-motor symptoms in the form of cognitive impairments, especially against the background of a comorbid pathology characteristic of cerebral ischemia [17]. Memory dysfunctions, the prevalence of which in the recovery period is a key pathogenetic link in the manifestation of residual organic and, as a result, functional lesions of the brain parenchyma [10, 11, 13].

The most important fundamental task after the restoration of vital functions in patients with stroke is a targeted impact on the “substrate” of the pathological condition, namely, those changes in the activity, shape and/or structure of the brain and the human body as a whole, which determine the formation of ischemic effects on the brain parenchyma, their stabilization and subsequent regression of altering influences during the post-stroke state. In cases of stroke patients, we are trying to trace what changes they have in the dynamics of the pathological state, in order to find out their determining features, to develop a

pathogenetically substantiated pharmacocorrection and preventive pharmacotherapy of possible non-motor complications in the early period of stroke.

It has been shown that mnemonic dysfunctions have a significant negative impact on the process of rehabilitation of patients with stroke [20]. It is known that in patients with persistent cognitive impairment in the post-stroke period, the prognosis for recovery is worse, and the recovery of neurological deficit takes longer, compared with those in patients without or with slightly less pronounced memory disorders [2, 20].

Therefore, since even after the restoration of the vital functions of the body, the cognitive deficit often persists, it is logical to assume that the pathology of the structures of the limbic system (LS) that determines it (cognitive deficit) and the complex afferent-efferent insufficiency of neurotransmission between the structures of the LS, the cerebral cortex and sensory systems is one of the candidates for the role of the "object" of cerebral ischemia and its consequences.

In order to correct mnemonic dysfunctions, some medications are used, the choice of which, although being made due to the understanding of the pathogenetic mechanisms of the disease is mostly empirical [3, 22]. At the same time, the preference in the ongoing therapy is given to polysensory afferentation for the activation of cognitive functions using both drug and non-drug means. More specifically, among the non-drug means specific attention is being paid to physiotherapeutic methods, namely magnetic therapy [1].

Among the effective drugs for the treatment of cognitive post-stroke disorders Phenibut stands out favorably (γ -amino- β -phenylbutyric acid hydrochloride), as a true nootropic of complex action with a wide range of pharmacological activity. The drug is classified as a tranquilonootropic one [14]. The possibility of long-term use at any age without side effects is largely due to the affinity for the natural metabolites of the body. In cases of post-stroke cognitive deficit, the following are especially important: adaptogenic, anti-stress, antiarrhythmic and hypotensive effects, improvement of cerebral hemodynamics in cerebral ischemia, normalization of autonomic regulation in cerebral angiodystonia.

Besides, Phenibut used for post-stroke convulsive syndrome and spasticity (due to its affinity with baclofen) [5-7].

The purpose: to investigate the fundamental mechanisms of brain ischemia in patients with mnemonic dysfunctions in the early recovery period of IS in people who have undergone COVID-19 through pharmacocorrection via Phenibut (γ -amino- β -phenylbutyric acid hydrochloride) and magnetic therapy.

Materials and methods

We examined 46 patients (28 men and 18 women, aged 40 - 60 years old) who had a history of confirmed COVID-19, and in the post-COVID period – IS with preservation of speech, writing, and confirmed by neuroimaging. The duration of IS at the time of inclusion in the study fluctuated within the early recovery period according to the well-known [4].

Patients were randomized into 3 clinical groups. The first (control) group consisted of 15 patients who were not prescribed nootropic drugs and physiotherapy procedures in the complex of rehabilitation. Patients of the second group (15 patients) at the stage of neurorehabilitation underwent magnetic stimulation procedures for 20 days (the frequency of basic impulses was from 180 to 195 Hz, the frequency of a group of impulses was in the range from 12.5 Hz to 29 Hz, the average induction of magnetic fields was in the range 100 μ T Patients of the third group (16 patients) additionally received Phenibut in one tablet (250 mg) 3 times a day.

The study of cognitive functions was carried out using a short scale of mental state – MMSE, a battery of tests for the study of frontal dysfunction – FAB, a test for memorizing 10 words according to the method of A.R. Luria and the clock drawing test. The geriatric depression scale (GDS) was used to study the emotional state. The testing in all groups was carried out twice, at the beginning of the study and after three months.

The obtained data were statistically evaluated by comparing the results of patients in the study groups with the results of the control (first) group, as well as between themselves, using the ordinal logistic regression model, in particular logistic regression with a cumulative relationship [9].

Results

During the survey, most patients noted a significant improvement. The improvement also concerned the intellect: it became easier to read newspapers, it became easier to communicate with the family. Studies on the MMSE scale in patients of the 2nd group after magnetic therapy showed an improvement in the results of 23.5 \pm 0.7 points vs 22.4 \pm 0.8 points in the control ($p>0.05$). Analysis of the results of individual subtests of the MMSE scale showed that in patients of the 2nd group, the result of the subtest “Voluntary attention” improved (3.8 \pm 0.3 points vs 3.1 \pm 0.2 points in the control group; $p<0.05$). Improvement in the test for the study of frontal dysfunction FAB – 15.2 \pm 1.2 vs 11.3 \pm 1.1 in control ($p<0.05$), while after treatment those cognitive functions, that were determined by “Speed of Speech”, “Simple Choice Reaction” and “Difficult Choice Reaction” subtests, recovered better.

In patients of the 3rd group, who received Phenibut, an improvement in cognitive functions was found in the MMSE tests (26.1 ± 0.8 points vs 22.1 ± 0.6 in the control; $p < 0.01$) and FAB (14.1 ± 0.1 points vs 11.3 ± 0.4 points in control; $p < 0.001$).

Significantly better were the results on the “Voluntary attention” (3.8 ± 0.1 points vs 3.1 ± 0.1 points; $p < 0.05$) and “Memory” (2.6 ± 0.2 vs 0 ± 0 points; $p < 0.05$) tests. In the test for memorization of 10 words, the difference in performance compared with the control after Phenibut treatment was in each subsequent presentation: 0.63 ± 0.02 , 1.52 ± 0.05 , 1.89 ± 0.05 words, in delayed presentation 1.75 ± 0.05 (in all cases $p < 0.001$). In the 2nd group, there was a trend towards improvement ($p > 0.05$).

Taking an investigational nootropic drug and magnetic therapy led to an average improvement of MMSE results. The influence of Phenibut turned out to be significantly better – the odds ratio compared to the control was 13.1.

Comparison of the results of the neuropsychological study with the FAB test battery showed that the pharmacocorrection methods used contributed to the improvement of the FAB results. The Phenibut nootropic drug turned out to be statistically significant – $p < 0.001$.

Taking into account the high influence of the emotional state on mnemonic functions, the antidepressant effect of nootropic drugs and magnetic therapy was evaluated. The best results were established in patients of the 3rd group compared with the results of patients of the 2nd and control groups.

Discussion

Therefore, our data indicate that the use of the proposed methods of treatment in stroke patients who suffered during the post-COVID period leads to a regression of depressive symptoms and is characterized by a decrease in the GDS score, and the use of Phenibut adds even a statistical significance.

Consequently, the regression of the clinical signs of stroke, and hence the increased severity of sanogenetic effects, does not always contribute to the normalization of mnemonic (cognitive) functions, especially in the context of a COVID-19 infection. This, on the one hand, shows their great latency in terms of normalizing the functioning of neurons, and, on the other hand, demonstrates the first functional “target”, the development of pharmacocorrection methods, which in the post-stroke period should be studied with particular accuracy. Taking into account the ability of post-stroke cognitive impairments to recovery, the different rates of recovery of neuronal functions in individual areas of the cortex and subcortical formations of the brain, as well as the strictly limited time frame of the post-

stroke period, the purposeful use of certain therapeutic measures at the stage of rehabilitation is of high importance. Special interest is to be directed at the maximum recovery of mnemonic dysfunctions, since we present it as one of the possible candidates for the “substrate” of cerebral ischemia.

Further research on the correction of cognitive deficit in the post-stroke period should be directed at the study of the effects of combined use of Phenibut and magnetic therapy to identify possible potentiating and synergistic effects.

Conclusions

Pharmacological and physiotherapeutic treatment use in stroke patients complex treatment who suffered during the post-COVID period results in depressive symptoms regression and characterizes by GDS score decrease. Phenibut use in these conditions has even a statistically proved clinical significance.

Stroke clinical signs regression and the increased severity of sanogenetic effects do not contribute to cognitive functions normalization, especially in the context of a COVID-19 infection.

Assuming the ability of post-stroke cognitive impairments to recovery, the different rates of neuronal functions recovery in certain cortical and subcortical areas together with the strictly limited post-stroke time interval one could suppose high importance of both pharmacological and physiotherapeutic treatment in stroke patients during the post-COVID period at the stage of rehabilitation.

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