NEW POSSIBILITIES IN THE TREATMENT OF PATIENTS WITH DISCIRCULATORY ENCEPHALOPATHY: FOCUS ON NERVE GROWTH FACTOR

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Summary

This study has shown the results of research on the role of neuronal growth factors in the development and progression of cognitive and psychoemotional disorders. The peculiarities of Bacopa Monier and Ginkgo Biloba influence on structural and functional changes of the brain in the experiment and in certain groups of patients have been shown. The results of the use of phytocomplex Memostim® (fixed combination of Bacopa Monier - 150 mg and Ginkgo Biloba - 120 mg) in 30 patients with II stage dyscirculatory encephalopathy (DE), caused by atherosclerosis and arterial hypertension are described. The control group involved 30 patients with II stage DE who were not treated with Memostim®. After 3 months of using Memostim® a decrease in the frequency and severity of cephalic, vestibulo-atactic and asthenic syndromes was observed in patients. There was a significant improvement in cognitive functions (MoSA scale) and psycho-emotional state of patients. There was a significant improvement in operations and attention (by 22% relative to baseline, $p < 0.05$) and the overall score on the test (+ 8%, $p > 0.05$). The general tendency to improve visual-constructive functions, memory, speech, executive functions, abstract thinking and orientation has been identified. Similar results of the effect of Memostim® on cognitive functions were obtained from FAB questionnaire. According to the results of the survey of patients on the scale of quality of life, a significant positive dynamics of the integrative index (statistically significant increase by 31%), index of psychological well-being (increase by 32%), self-satisfaction (by 28%), indicators of physical well-being (by 18%) after 3 months of using Memostim® has been established. The level of neuronal growth factor (β-NGF) has significantly increased (by 67%). The analysis of the obtained data testifies to the effectiveness and safety of Memostim® when used in patients with DE. Thus, the obtained data demonstrate the profound effect of Memostim® on the symptoms of cognitive and psychoemotional disorders in patients with DE, due to increased NGF levels on the background of the course.

Keywords: phytocomplex Memostim®, dyscirculatory encephalopathy, cognitive disorders, psychoemotional state, neuronal growth factor.

Introduction.

According to the World Health Organization, the problem of vascular diseases of the brain is one of the most pressing issues in clinical medicine, associated with the dynamic aging of the world's population and the growing risk factors of cerebrovascular disease (CVD) [1].

Among all forms of vascular pathology of the brain, chronic circulatory disorders are the most common and often precede the development of stroke or dementia. In Ukraine, the term "dyscirculatory encephalopathy" (DE) is used to denote chronic cerebrovascular insufficiency [2]. Although the term originated in the 1960s, it is still used today due to its clinical significance. Other similar definitions that have a syndromic or nosological meaning are chronic cerebral insufficiency, chronic vascular insufficiency, slowly progressive cerebral insufficiency, cerebrovascular disease, chronic cerebral ischemia, etc. In some countries, the analogues of term DE are as follows: vascular cognitive impairment, vascular neurocognitive impairment, vascular dementia, lacunar brain and others. Risk factors for chronic vascular pathology of the brain include: old age, negative man-made

effects, social and personal stress, bad habits (smoking, alcohol abuse), malnutrition, obesity, hypodynamics, hypertension, hypotension, diabetes mellitus, heart disease (arrhythmias, valve lesions, myocardial infarction, etc.) [3].

The development of DE is based on the pathology of large and small vessels of the brain [2,3]. But the most common cause is considered to be damage to small vessels of the brain (microangiopathy) [3,4]. Lesions of the cerebral arteries may be accompanied by microembolization of the distal bed and the possible development of microinfarctions. The cause of DE may be cardiac pathology with heart failure and decreased cerebral perfusion and cerebral vein lesions as well. It should be noted that in a significant number of patients, especially the elderly, cerebrovascular pathology can initiate or exacerbate neurodegenerative processes (more often associated with the deposition of β-amyloid protein (β-AB)) [5].

The core of clinical manifestations of DE, along with neurological syndromes, are cognitive impairments that significantly affect the quality of life of patients [6,7]. A special feature of neurocognitive disorders (NCD) is the dominance in the structure of disorders of regulatory control functions, which are provided by the interaction of cortico-subcortical structures and the frontal cortex [3-7]. The quality of cognitive functions is directly related to the activity of neurotrophic factors (NTFs). NTFs are a large and heterogeneous group of polypeptides (up to 200 amino acid residues) produced by brain tissue and play a key role in the development and maintenance of structures of the central and peripheral nervous system. They participate in the regulation of growth, development, differentiation and survival of cell populations and the processes of their adaptation to external influences [8; 9].

In the 1960s, Rita Levy-Montalcini and Stanley Cohen discovered neuronal growth factor (NGF), which is included in neurotrophic factors.

The authors were awarded the Nobel Prize for discovering this factor. The neutrotrophic effect of NGF is to stimulate the growth, differentiation, development and survival of neurons. It is mediated by interaction with Trka and p75 (NTR) receptors. In the brain, NGF is formed in structures innervated by cholinergic neurons of the basal ganglia of the forebrain [9] and is retrogradely transported by axons to the neuronal stroma. NGF is required for normal plastic rearrangements during the development and functioning of mature neurons of the basal cholinergic nuclei of the forebrain. Trophic support of NGF cholinergic neurons helps to maintain a sufficient number of them. Also it stabilizes the level of activity of key enzymes of acetylcholine synthesis and affects the volume and quality of cortico-subcortical connections. These processes are important for learning, memory and other cognitive functions [10].

There is a suggestion of impaired NGF trophic support of cholinergic neurons of the basal ganglia of the forebrain in Alzheimer's disease and chronic cerebral ischemia, and the possibility of using this factor as a potential therapeutic agent. However, the therapeutic use of NGF itself is limited by its low ability to cross the blood-brain barrier, the possibility of an immune response, and the presence of side effects due to its pleiotropy. Probably because of this, experimental and clinical attempts to use NGF to correct pathological processes caused by brain injury or Alzheimer's disease have not given any positive results. An important approach to the regulation of trophic factors in the central nervous system is the creation of mimetics of NGF, which stimulate its release or interact with the appropriate receptors.

There are many methods to improve cognitive function by affecting NGF release. One of them is Bacopa monnieri and Ginkgo biloba extracts [11-15].

Many studies have shown the effectiveness of Ginkgo Biloba extract in improving memory, concentration and stability of attention, associative processes and psychomotor functions. Against the background of taking Ginkgo Biloba there is an improvement in health (decrease in frequency and severity of cephalgia, dizziness, noise in the head), restoration of sleep structure [11-15]. According to research, effective correction of cognitive impairment is achieved by a course of Ginkgo Biloba extract in a daily dose of 240 mg (120 mg twice a day) [16]. But the use of Ginkgo

Biloba does not always effectively affect the cognitive impairment and psycho-emotional state of patients [18]. Therefore, the addition of Bacopa Monier to Ginkgo Biloba may have a greater impact on these processes and is a promising tool in the treatment of patients with neurocognitive disorders, including patients with chronic cerebral ischemia.

A sufficient number of experimental and clinical studies have been performed. They have confirmed the effectiveness of Bacopa Monier in the correction of cognitive impairment. Thus, experimental studies have demonstrated the ability of Bacopa Monier to increase NGF levels in various brain structures: by 47.5% in the hippocampus, and by 108.7% in the prefrontal cortex [16-23]. Bacopa Monier's ability to increase the concentration of NGF in blood plasma and cerebrospinal fluid has also been shown in patient studies, apparently as a result of increased expression of this neurotrophin in the brain's tissues. Since NGF is a trigger for neuronal tissue repair, an increase in its level with Bacopa Monier extract was also accompanied by an increase in the release of other neurotrophins, in particular BDNF [23]. This increase in the activity of neurotrophic factors on the background of Bacopa Monier was associated with increased neurogenesis in the subventricular zone of hippocampus, which was accompanied by a significant weakening of dementia symptoms [19-23]. This indicates the ability of Bacopa Monier to enhance regenerative processes in the brain.

In addition to the effect on the level of NTF, especially NGF, Bacopa Monier extract is characterized by additional mechanisms of neuroprotective action: increasing the activity of the antioxidant defense system (both enzymatic and non-enzymatic units), normalization of neutrotransmitters, glutamate, 5-hydroxytryptamine, dopamine) in various structures of the brain, strengthening of blood supply of the brain by NO-mediated dilatation of cerebral vessels [22; 23]. An important component of the positive effect of Bacopa Monier on neurocognitive functions is the ability to inhibit the activity of acetylcholinesterase (ACE) comparable in strength to specific inhibitors of this enzyme (donepezil and rivastigmine). As a result, Bacopa Monier promotes the accumulation in hippocampus of the main memory neurotransmitter - acetylcholine, increases the expression of M1-cholinoreceptors and reduces β-AB. Such effect of Bacopa Monier extract may be due not only to direct interaction with ACE (its suppression), but rather to the consequence of increased release of NTF (primarily NGF), which has a positive reciprocal (reverse) effect on the cholinergic system of hippocampus. Bacopa Monier has been shown to have a significant nootropic effect, which improves memory (long-term, short-term, logical) and attention. Bacopa's multimodal effect on memory processes is based on the ability of biologically active substances of the plant to optimize the processes of monoamine potentiation (serotonin and dopamine), synthesis and receptor interaction of acetylcholine and GABA, which allows to harmonize short-term and long-term memory, reaction rate cognitive process, associative thinking, ability to learn, memorize, concentration and speed of switching attention. A number of studies have shown that Bacopa Monier extract protects the hippocampal pyramidal cells from cerebral ischemia, normalizes the functions of ATP-dependent enzymes, thereby improving cognitive function and stimulating the formation of new neuronal connections (neuroplasticity) and increasing neuronal density in hippocampus. According to study results, effective correction of cognitive impairment is achieved by a course of Bacopa Monier extract at a dose of 300 mg / day (150 mg twice a day) [19].

In addition to protecting the brain's tissue from pathogens (neuroprotection), in parallel with the activation of the formation of new nerve cells (neurogenesis), Bacopa Monier stimulates plastic transformations in the brain that promotes the formation of new neuronal connections. The last property of Bacopa Monier is due, in particular, to its positive effect on the transcriptional factor CREB (cAMP response element-binding protein), which is a consequence of increased expression of receptors with which NGF interacts - tyrosine kinase A (TrkA). Unlike many NTF mimetics, Bacopa Monier is able not only to stimulate the formation of NGF itself, but also to increase the number of specific receptors with which this neurotrophin interacts. This fact is of great clinical importance, because to implement the neurotrophic action of NGF is not enough to increase its level, but it is necessary to ensure interaction with TrkA membrane receptors and trigger intracellular metabolic

reactions, which will result in maintaining normal neuronal function (neuroprotection), stimulating their formation) and adequate interneuronal interaction (neuroplasticity). As of today, the positive effect of Bacopa Monier extract on the cognitive functions of patients has been proven from the standpoint of evidence-based medicine. In particular, according to the results of a meta-analysis of double-blind randomized placebo-controlled clinical trials, Bacopa Monier extract significantly improves patients' cognitive functions.

In the pharmaceutical market of Ukraine, the combination of Bacopa Monier and Ginkgo Biloba extracts is presented in the form of phytonutropic complex Memostim®, which contains standardized extracts of Bacopa Monier - 150 mg and Ginkgo Biloba - 120 mg. In the pharmacodynamics of Memostim®, the neurotrophic effects of Bacopa Monier are successfully complemented by the positive effect of Ginkgo Biloba extract on cerebral microcirculation, which prevents the development of microangiopathy.

Thus, the assessment of clinical effectiveness of Memostim® in patients with II stage DE caused by atherosclerosis and hypertension, is very relevant and promising.

The purpose of the study: to study the dynamics of clinical and neurological, emotional and cognitive disorders, as well as the level of neurotrophic factors in patients with II stage DE on the background of taking Memostim®.

In accordance with the purpose, an open clinical study of the effectiveness of Memostim® has been performed in patients with II stage DE caused by atherosclerosis and hypertension.

Inclusion criteria:

- Patients (men and women) with a clinical picture of II stage DE.
- Age of patients 45-75 years.
- No medical contraindications for using phytocompositions based on Bacopa Monier and Ginkgo Biloba.

The study involved 60 patients with signs of II stage DE caused by hypertension and atherosclerosis. The mean age of patients was 53.2 ± 5.7 years. The main group consisted of 30 patients with II stage DE, who used Memostim® in addition to the basic therapy. The control group included 30 patients with II stage DE, who received basic therapy without using Memostim®. Patients were comparable in age and sex. Basic therapy in both groups was antihypertensive and hypolipidemic therapy. The study avoided the appointment of other drugs that affect metabolism and blood circulation in the brain (nootropic, neurotrophic, vasoactive drugs, etc.).

Memostim® was prescribed in the following dosage regimen: during the first month (base course) - 1 capsule twice a day after meals, for the next 2 months (maintenance course) - 1 capsule once a day after meals. The total duration of observation was three months. Examination of patients was performed before and after the course of Memostim® at the Department of Vascular Pathology of the Brain and Rehabilitation of the Institute of Neurology, Psychiatry and Addiction of the National Academy of Medical Sciences of Ukraine, Kharkiv.

To achieve this goal, the following methods were used: clinical-neurological, psychodiagnostic, biochemical, enzyme-linked immunosorbent assay and statistical.

Clinical trials have included detailed analysis of subjective and objective neurological manifestations of the disease.

The state of cognitive and psychoemotional functions of patients was determined by psychodiagnostic methods: Montreal Cognitive Assessment (MoCA), Frontal Assessment Battery (FAB), Spielberger test, Beck Depression Inventory (BDI), WHOQOL-BREF.

Determination of β-NGF levels in serum was performed by enzyme-linked immunosorbent assay using a specialized set of reagents (Beta-NGF; RayBiotech, Inc., USA). In patients of the main and control groups, β-NGF levels were measured at the beginning of the study and 3 months after the start of therapy. Statistical analysis of the results was performed using Student's t-test (significance of differences at $p \leq 0.05$).

Study results

The course of Memostim® had a positive and statistically significant effect on the dynamics of subjective complaints in patients with II stage DE caused by hypertension and atherosclerosis. The most pronounced decrease was in the intensity of headache, dizziness and problems with memorizing new information. There was a decrease in the number of complaints of memory disorders, asthenia and decreased attention. According to the health questionnaire, the positive effect of Memostim® was reported in 28 (93.3%, $p \leq 0.05$) patients. No complications or adverse reactions have been found in any of the patients involved in the study.

At the end of the 3rd month of the study, there was no improvement in the subjective symptoms of DE patients in the control group who did not receive Memostim®.

However, the dynamics of objective clinical symptoms on the background of the course of Memostim® has changed significantly. The most significant decrease was observed for asthenic syndrome (– 66% of the number of patients who had such symptoms at the beginning of the study, $p \leq 0.05$) and cognitive impairment syndrome (– 70%, respectively, $p \leq 0.05$). The course of Memostim® allowed to reduce the number of patients with cephalic syndrome (–56%, $p \leq 0.05$), vestibulo-atactic and cerebrospinal fluid-hypertension syndromes (– 43% for each syndrome, $p \leq 0.05$). Thus, the most pronounced positive effect of Memostim® was on the asthenic syndrome and impaired cognitive function of patients with DE.

In the control group, the dynamics of objective clinical symptoms was less pronounced and was observed only in the reduction of vestibulo-atactic (–4%, $p \leq 0.05$) and asthenic (–5%, $p \leq 0.05$) syndromes. Moreover, at the end of the study, an increase in the frequency of cephalic (+ 7%, $p \leq 0.05$) and cerebrospinal fluid-hypertension (+ 16%, $p \leq 0.05$) syndromes was registered in patients of the control group.

According to the results of Montreal Cognitive Assessment (MoSA scale) in patients of the main group after a 3-month course of Memostim® there was found a significant improvement in computational operations and attention (22% and 26% relative to baseline, $p < 0.05$) and total score from the test (+ 8%, $p > 0.05$). According to the test, there is a general trend to improve visual and constructive functions, memory, speech, executive functions, abstract thinking and orientation. Similar results of the effect of Memostim® on cognitive functions were obtained from FAB questionnaire. Memostim's® three-month course significantly improved conceptualization processes (+ 27%, $p > 0.05$), speech rate (+ 24%, $p > 0.05$), and grasping reflex (+ 22%, $p > 0.05$).

On the contrary, in the control group there was no significant dynamics in the improvement of neurocognitive functions according to the results of MoSA and FAB scales.

According to the monitoring of psycho-emotional state on Beck Depression Inventory on the background of taking Memostim® a positive dynamics of cognitive-affective and somatic component has been established in patients with DE. Somatic manifestations of depression had a positive dynamics in almost all patients of the main group (the data were normalized in 40% of patients, $p > 0.05$; and in 56% of patients – transformed into a mild form, $p > 0.05$). During 3 months of using Memostim® in patients of the main group, the state of emotional tension, indicators of personal and reactive anxiety according to the Spielberg questionnaire significantly decreased (decrease by 20% and 19%, respectively, $p > 0.05$). Thus, moderate antidepressant and anti-anxiety effects of Memostim® were observed in the examined patients, apparently due to Bacopa Monier. These results correlate with data from the scientific literature, according to which the content of NGF in blood plasma decreases in patients with anxiety and depressive disorders and returns to normal after a course of treatment [30].

In the control group, significant positive changes in the emotional sphere during 3 months of the study did not occur.

The dynamics of the reduction of subjective complaints of psycho-neurological symptoms in patients who participated in the study correlated with an increase in NTF – β-NGF. Thus, as a result of the study it was found that on the background of taking Memostim® for 3 months the level of β-

NGF in the blood of patients of the main group increased significantly by 67% compared with the beginning of the study (p <0,05, Fig. 1) and 68% (p <0.05, Fig. 1) compared with the control group at the end of the study. In our opinion, this indicates the ability of Memostim® to enhance reparative processes in the brain in the course of use in patients with II stage DE.

It should be noted that in the group of patients who received Memostim® in addition to the basic therapy, the increase in β-NGF was the same between the subgroups of men and women.

In the control group (both men and women) there were no significant changes in serum β-NGF before and at the end of the study.

At the same time, in the group of patients with DE with hypertension, there was found that on the background of taking Memostim® for 3 months, the level of β-NGF in the blood of patients in the main group increased significantly by 56% compared with the beginning of the study (p <0,05, Fig.2) and 51% (p <0.05, Fig.2) compared with the control group at the end of the study. In our opinion, this indicates the ability of Memostim® to provide neuroprotection in the course of use in patients with II stage DE and concomitant hypertension.

There were no significant changes in β-NGF in serum in the control group before and at the end of the study.

Against the background of taking Memostim® for 3 months, in a subgroup of patients with DE caused by atherosclerosis, there was found that the level of β-NGF in the blood of patients in the main group significantly increased by 61% compared with the beginning of the study (p <0,05 Fig.3) and 57% (p <0.05, Fig.3) compared with the control group at the end of the study.

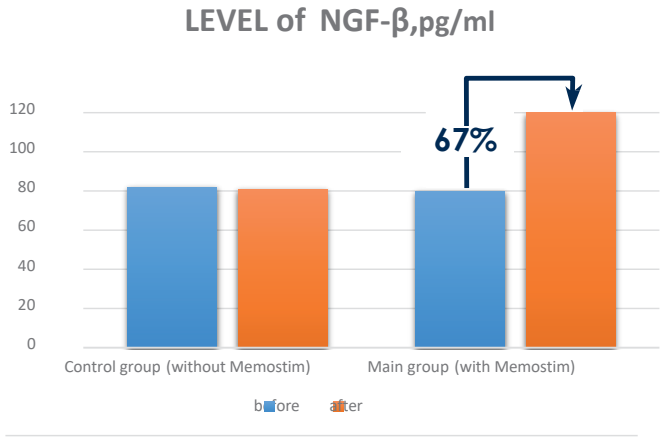
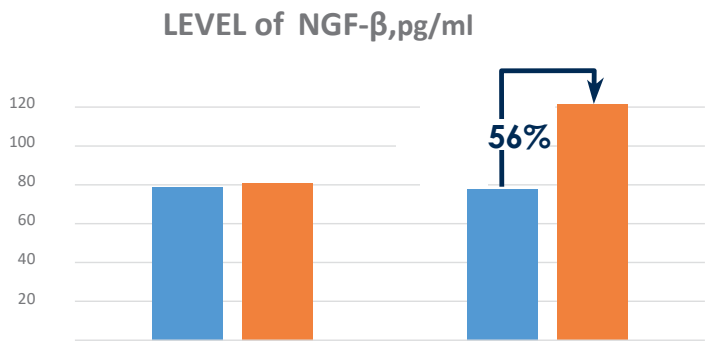


Figure 1. The level of β-NGF (pg/ml) in the serum of patients before and after the study



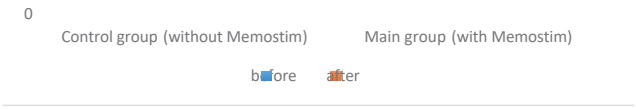


Figure 2. The level of β-NGF (pg/ml) in the serum of patients with DE and hypertension before and after the study

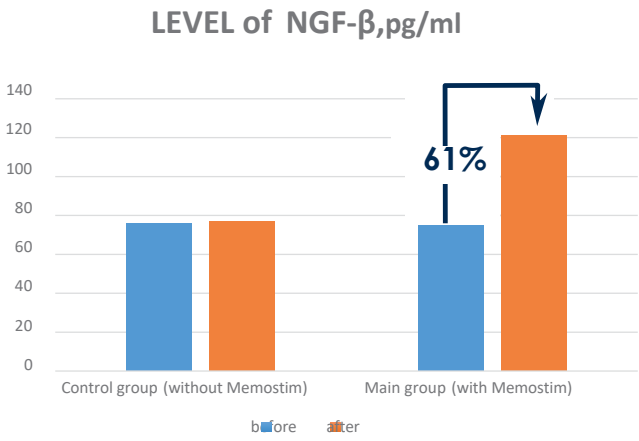


Figure 3. The level of β-NGF (pg/ml) in the serum of patients with DE and atherosclerosis before and after the study

In our opinion, this indicates the ability of Memostim®, primarily due to Bacopa Monier extract, to have a neuroprotective effect, normalization of neutrotransmitter levels in various structures of the brain, strengthening the blood supply of the brain by NO-mediated dilatation of cerebral vessels, which correlates with scientific literature [27, 29]. There were no significant changes in serum β-NGF in the control group before and at the end of the study.

The study has found a relationship between the increased levels of β-NGF in the serum of patients with DE of different ages. Thus, in the group of patients with II stage DE aged 45-60 years who took Memostim® for 3 months, the content of NGF in the serum increased by 57% ($p < 0.05$) from baseline.

Accordingly, in the group of patients with II stage DE aged 60-75 years, who took Memostim® in a similar mode, the content of NGF in the serum increased by 50% ($p < 0.05$) from baseline. Thus, the stimulation of neurotrophic processes by Memostim® is most pronounced in the middle age group of patients, which demonstrates faster activation of regenerative processes in the nervous system in patients of working age and is of great social importance. This creates the preconditions for using Memostim® in order to reduce the progression of DE with age.

In the control group, there were no significant changes in β-NGF in serum in patients with DE of different ages before and at the end of the study.

The obtained data demonstrate the complex effect of Memostim® on the symptoms of cognitive and psychoemotional disorders in patients with DE, the pathogenetic basis of which are closely related to the normalization of β-NGF on the background of taking Memostim®. The obtained results may be mediated by the effect of Memostim® components on NTF, in particular, Bacopa Monier extract. Similarly, according to the literature, Bacopa Monier extract by modulating the action of NTF, including NGF, provides full neuroprotection and neurotransmission, and normalizes the processes of neurogenesis and neuroplasticity as well [32-35].

According to the results of a survey of patients receiving Memostim® on QOL indicators, a significant positive dynamics of the integrative index (+ 31%, $p < 0.05$), the index of psychological well-being (+ 32%, $p < 0.05$), the level of self-satisfaction (+ 28%, $p < 0.05$), indicators of physical well-being (+ 18%, $p < 0.05$) has been established. Subjectively high assessment of QOL by patients

on the background of taking Memostim® can be interpreted as a positive predictor of patients' high compliance with medical recommendations.

Thus, the course application of Memostim®, due to the presence of Bacopa Monier and Ginkgo Biloba extracts, has a positive effect on the psycho-emotional state, memory, attention, speech and other cognitive functions of patients.

CONCLUSIONS

1. The use of Memostim® on the background of basic therapy has shown effectiveness in patients with II stage DE. This was manifested, in particular, by a statistically significant increase in serum β-NGF levels by 67% in patients of the main group. Patients in the control group did not experience positive dynamics.
2. The use of Memostim® for 3 months has shown a statistically significant increase in serum β-NGF levels in the subgroups of DE patients with hypertension by 56%, and DE patients with atherosclerosis - 61%. Similar dynamics did not occur in patients of the control group.
3. The use of Memostim® for 3 months has significantly reduced the subjective and objective manifestations of DE. In most patients, the intensity of complaints has decreased from 4 to 1-2 points, and in a significant number of patients a complete reduction in the intensity of clinical symptoms and increased subjective assessment of certain parameters of QOL have been reported.
4. The course reception of Memostim® in patients with II stage DE was characterized by positive dynamics in the cognitive sphere, namely the improvement of mnestic indicators, the characteristics of voluntary attention and increased effectiveness of mental activity in general.
5. The positive effect of Memostim® on the psycho-emotional state of patients, reduction of emotional and affective disorders in the form of mood stabilization, weakening of anxiety-depressive component and asthenia have been established.
6. Analysis of the obtained data suggests that Memostim® is an effective and safe preparation for patients with II stage DE, and can be recommended for widespread use to correct cognitive dysfunction due to chronic cerebrovascular disorders.

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