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.

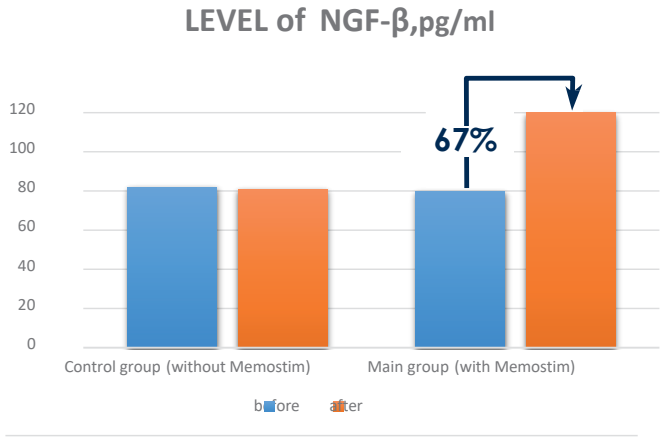
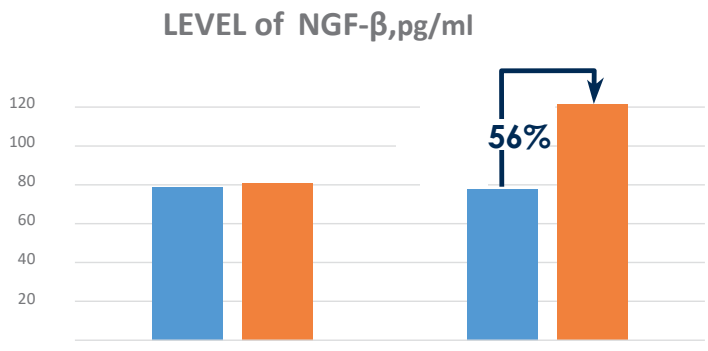


Figure 1. The level of β-NGF (pg/ml) in the serum of patients before and after the study



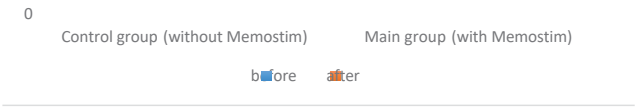


Figure 2. The level of β-NGF (pg/ml) in the serum of patients with DE and hypertension before and after the study

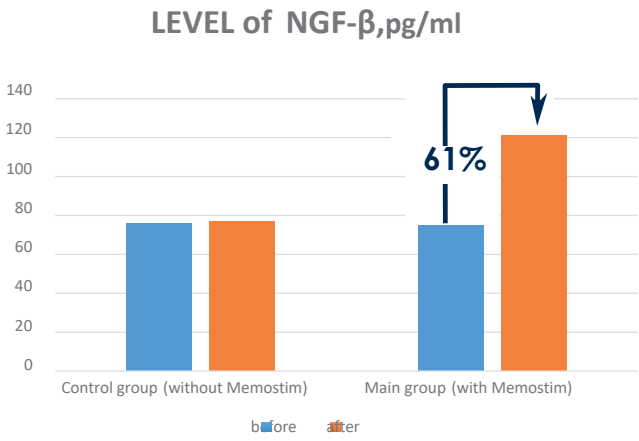


Figure 3. The level of β-NGF (pg/ml) in the serum of patients with DE and atherosclerosis before and after the study

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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NEW OPPORTUNITIES IN THE TREATMENT OF PATIENTS WITH DYSCIRCULATORY ENCEPHALOPATHY, CAUSED BY METABOLIC SYNDROME

Summary

The article presents the results of a clinical study examination the efficacy and tolerability of the use of fixed phytocomposition Memostim (Ananta Medicare, United Kingdom) in patients with dyscirculatory encephalopathy (DE) stage II, caused by metabolic syndrome. The phytocomposition was given to the Substitutes in 30 patients with DE stage II with metabolic syndrome (main study group) within 3 months. Patients received 1 capsule 2 times a day during the first month, then 1 capsule 1 time per day for two months. The comparison group consisted of 30 patients with DE stage II with a metabolic syndrome, where phytocomposition Memostim was not add to the standard course of therapy. Efficiency and safety of phytocomposition of the Memostim were assessed on the basis of clinical neurological, psychodiagnostical, biochemical, immunoenzymatic, and statistical methods. After three months of treatment, a significant decrease in the frequency and intensity of clinical and neurological manifestations of the disease was observed, and a positive dynamics in the neurocognitive sphere, psycho-emotional state of patients was noted. The concentration of the human nerve growth factor (NGF-β) increased for 67 %, which indicated the recovery of neuroplasticity.

Keywords: dyscirculatory encephalopathy, metabolic syndrome, cognitive impairment, phytocomposition Memostim, treatment

Introduction

According to the World Health Organization, the problem of cerebrovascular disease (CVD) is becoming the most pressing problem of clinical medicine, due to the aging of the world's population and increasing prevalence of CVD risk factors in the population [1]. As in other countries, this problem is relevant in Ukraine. Over the past 10 years, the number of patients with CVD in our country has doubled: currently the incidence exceeds 8,200 cases per 100,000 population, due to an increase in the proportion of both strokes and chronic forms of cerebral disorders. Today more than 2.5 million people suffer from CVD of varying severity in Ukraine. Almost 100,000 new stroke cases occur in the country every year. In the structure of CVD, 4-5% are acute conditions, the rest – 95-96% – chronic cerebrovascular disorders [2].

To define chronic cerebrovascular disorders in clinical practice in our country, the term with the nosological meaning "dyscirculatory encephalopathy" (DE) is used. Dyscirculatory encephalopathy is a slowly progressive diffuse and focal lesion of the brain due to chronic deterioration of cerebral circulatory disorders. Although the term originated in the 1960s, due to its clinical significance, it is still used today. Other similar definitions that have a syndromic or nosological content are chronic cerebral insufficiency, chronic cerebrovascular insufficiency, slowly progressive cerebral insufficiency, cerebrovascular disease, coronary heart disease, etc. In some countries, the term "dyscirculatory encephalopathy" is used instead of "vascular dementia", "vascular cognitive impairment".

As for the International Classification of Diseases of the 10th revision (ICD-10), the diagnoses - analogues of DE are as follows: 167.2 - cerebral atherosclerosis, 167.4 - hypertensive encephalopathy, 167.9 - unspecified vascular diseases.

Dyscirculatory encephalopathy (DE) is characterized by two qualitative features: gradual development in some cases (long period of clinically "hidden" course) and multifocal brain damage due to damage to small and large cerebral vessels (cerebral microangiopathy, macroangiopathy) [4]. In addition, the cause of DE can also be cardiac pathology with heart failure and decreased cerebral perfusion, cerebral vein lesions and others. At the same time, in a large number of patients,

especially the elderly, cerebrovascular pathology can initiate the intensification of degenerative processes, more often associated with amyloid deposition [4, 5].

Risk factors for developing DE are the same as for stroke, and include hypertension (AH), atherosclerosis, diabetes mellitus, heart disease (arrhythmias, valve damage, myocardial infarction, etc.), negative man-made impacts, social and personal stress, harmful habits (smoking, alcohol abuse - more than 30 standard units per month), malnutrition, obesity, hypodynamics [6].

Among the risk factors of DE, much attention is paid to the metabolic syndrome (MS), the main components of which are the abdominal form of obesity, namely - waist circumference in men is more than 94 cm, in women – more than 80 cm; the presence of hypertension (blood pressure is higher than 140/90 mm Hg or the use of antihypertensive therapy); increase in serum triglycerides above 7 mmol/l; decrease in the level of high-density lipoproteins less than 1 mmol/l for men and less than 1.2 mmol/l for women; increase in fasting plasma glucose levels above 5.6 mmol/l or treatment of hyperglycemia.

The main components of MS belong to the modified risk factors. In individuals with 2-3 components of MS, new episodes of cerebrovascular complications during five years of follow-up were found in 2.5% of patients. This is more common than in patients without signs of MS. In individuals with 4 or more components of MS, 14.9% of patients had five years of follow-up. It is proved that in the presence of MS the frequency of cerebral pathology is 4 times higher than in cases of cardiac pathology [7, 8].

Due to the steady increase in the prevalence of MS over the next 20 to 30 years, according to the WHO, clinicians should expect a rapid increase in the prevalence of CVD in the population.

An additional factor in the unfavorable course of CVD is a violation of carbohydrate metabolism and, above all, the emergence of insulin resistance, which contributes to the violation of metabolism in the vascular wall and the development of atherosclerotic complications [9].

MS is also accompanied by pronounced changes in the main macroreological characteristics - blood viscosity, hematocrit, fibrinogen, and the aggregation properties of blood cells as well. In patients with MS, compared with those without it, there is a more accelerated formation of erythrocyte aggregates with increased strength. Thus, MS adversely affects all parts of atherothrombogenic activity of the vascular wall (antiplatelet, anticoagulant, procoagulant and fibrinolytic), causing their discoordination at the initial stage of CVD [10].

A special feature of the clinical course of DE in patients with MS is the presence of neurological symptoms and syndromes, neurocognitive disorders (NCD) of varying severity [11, 12].

It has been proven that NCD in patients with MS is observed 20% more often than in the general population, and is associated with other manifestations of MS, primarily with the level of dyslipidemia, high blood pressure, degree of insulin resistance and obesity. A number of studies have shown that patients with MS have an increased risk of developing NCD, both pre-dementia and those that reach the degree of dementia [13, 14].

Therefore, taking into account the multifactorial pathogenesis of DE caused by MS, the treatment program in such patients should be comprehensive and include measures to prevent further damage to cerebral vessels, to improve and stabilize neurocognitive and psychoemotional functions, and to correct existing metabolic disorders as well [15, 16].

Recently, phytopreparations are widely used for the treatment of NCDs, which have a complex effect on all components of DE due to antioxidant, hypolipidemic, nootropic, antidepressant, anxiolytic and metabolic actions. They have a high level of evidence base and affect the restoration of impaired functions effectively [17].

The use of complex herbal remedies for the correction of cognitive impairment allows effective and long-term monitoring of the progression of dysfunction and helps to increase compliance with the high safety profile, good tolerability of natural ingredients and low risk of inter-drug interactions.

This combination is presented in the modern fixed phytocomposition Memostim (by Ananta Medicare, UK). Polymodality of clinical effects, broad evidence base and good tolerability of

Ginkgo Biloba and Bacopa Monier medicinal extracts are a solid basis for their combined use in patients with CVD in therapeutically justified doses (120 mg and 150 mg, respectively). The effectiveness of medicinal extracts of Ginkgo Biloba and Bacopa Monier has been proven in the treatment of many diseases [18]. However, their effectiveness and safety in patients with DE have not been studied. Therefore, the study of clinical efficacy and tolerability of the phytocomplex Memostim (Memostim) is very relevant and will help to improve the therapeutic strategy and rehabilitation of patients with DE caused by MS.

The purpose of the study: to study the efficacy, tolerability and safety of Memostim (Ananta Medicare, UK) in patients with II stage DE caused by MS.

To solve the goal and objectives of the study, an open study of the effectiveness, tolerability and safety of Memostim in patients with II stage DE caused by MS has been performed.

Memostim was used in 30 patients with II stage DE caused and MS (19 women, 11 men, aged 45 to 75 years), who formed the main group of the study. Complaints, anamnestic data, a physical examination, anthropometric parameters were collected in the patients. Also waist circumference (cm), body weight (kg) and height (m) were used to calculate body mass index. Clinical signs of MS were present in the examined patients of the main group. All patients of this group on the background of the standard course of therapy for 3 months took Memostim 1 capsule twice a day in the first month of the study and 1 capsule once a day for the second and third month.

The comparison group consisted of 30 patients with II stage DE, also due to MS, to the standard course of therapy which was not added Memostim. General characteristics of the groups of examined patients are shown in table 1.

Table 1. Characteristics of the examined patients in groups

Parameter	Main group (n=30)	Comparison group (n=30)
Men	11	16
Women	19	14
Age, years	52.7 ± 5.8	53.1 ± 6.2
Body mass, kg	84.1 ± 13.9	82.9 ± 12.0
Waist, cm	89.8 ± 8.8	84.8 ± 8.9
Body mass index	29.9 ± 4.05	28.7 ± 1.9

Thus, both groups of patients, stratified by the presence of signs of MS, were comparable in age and gender that allows their comparative analysis to establish certain patterns of influence of Memostim on the clinical manifestations of the disease and metabolic processes.

The patients, enrolled in the clinical trial, stayed on basic antihypertensive, hypoglycemic and hypolipidemic therapy, but were not prescribed drugs with vasoactive, neurometric, and nootropic effects. All examined patients gave informed consent to conduct this study.

The following research methods were used to solve the set goals and objectives of the study: clinical-neurological, psychodiagnostic, biochemical, statistical, enzyme-linked immunosorbent assay. Clinical trials have included detailed analysis of subjective and objective neurological manifestations of the disease.

Assessment of the state of cognitive functions was performed using psychodiagnostic studies:

Montreal Cognitive Assessment (MoSA), Frontal Assessment Battery (FAB). To assess the psycho-emotional state used Beck Depression Inventory and Spielberger Scale. Quality of life was assessed using the WHOQOL-BREF.

Clinical laboratory studies were performed according to standard methods (general blood test, general urine test, biochemical blood test, coagulogram, lipid profile; determination of fasting glucose and insulin levels).

To determine the effect of Memostim on some parameters of neuroplasticity, human nerve growth factor β-NGF was determined before and after the study. The last was determined by enzyme-linked immunosorbent assay using a specialized set of reagents (Beta-NGF, manufactured by Ray Biotech, Inc., USA). Sensitivity of the method – the minimum set dose of Beta-NGF is less than 14 pg/ml. Blood for the study was taken on an empty stomach, 12 hours after the last meal, in patients of the main group before the appointment of Memostim and at the end of a 3-month course of its use.

According to the study design, monitoring of clinical status and key laboratory parameters was performed twice (at the beginning and end of the course of taking Memostim in patients of the main group) and after 3 months in patients of the comparison group. Control of tolerability and the presence of adverse events were performed during 3 months of follow-up (according to individual surveys and the patient's diary).

Statistical processing of the study results was performed using standard programs of Rentium III-500 and applications such as Excel and Statistica, which included standard methods of variation statistics - calculation of average values (M), standard statistical error of average values (m). Under the conditions of normal data distribution, the differences between the groups were determined using Fisher's φ-test (the probability of differences is at $p < 0.05$).

Carrying out a thorough clinical and neurological examination of patients in the main group and the comparison group made it possible to assess the clinical manifestations of II stage DE caused by MS, before and after the use of Memostim (Table 2).

Table 2. The effect of Memostim on the dynamics of subjective symptoms in the examined patients of the main group

Subjective symptoms	Main group (n=30)				Comparison group (n=30)				φ_1	φ_2
	Before using Memostim		After using Memostim		Basic data		After 3 month of treatment			
	abs.	%	abs.	%	abs.	%	abs.	%		
Headache	28	93.3	18	60	26	86.6	30	100	3.281*	2.895*
Dizziness	29	96.7	14	46.6	27	90	29	96.6	4.920*	1.070
Tinnitus	27	90	12	40	25	83.3	26	86.6	4.371*	0.362
Sleep disorders	25	83.3	10	33.3	24	80	29	96.6	4.142*	2.169*
Fatigue	26	86.7	19	66.3	24	90	25	83.3	2.143*	0.334
Memory impairment	27	90	18	60	26	86.6	30	100	2.812*	2.895*

Note: * – $\varphi \geq 1.65$

The most pronounced and common complaints among patients of the main group were headache, which was reported in 28 patients (93.3%) (various nature and severity: from discomfort in the head to severe diffuse headache), noise, ringing in the head - in 27 patients (90%), dizziness - in 29 patients (96.7%); decreased memory - in 27 patients (90%), decreased efficiency, attention, mood swings, irritability, fatigue - in 26 patients (86.7%). There were also complaints of shakiness when walking ("the ground goes from under your feet"), slowing of intelligence ("difficult to gather thoughts"), and inattention. Deterioration of general condition was accompanied by deterioration of sleep in 26 patients (86.7%): difficult to fall asleep, restless sleep with frequent awakenings, nightmares, lack of feeling of rest after sleep.

In patients of the comparison group, the subjective manifestations did not differ from those in the main group (see Table 2).

In patients of the comparison group who did not receive Memostim, there was a slight worsening of the subjective symptoms of DE at the end of the 3rd month. At the same time, the use of Memostim for 3 months in patients of the main group contributed to a significant reduction in the

main subjective manifestations of DE. Symptoms such as headache, dizziness, tinnitus, sleep disturbances, fatigue, and memory impairment decreased most significantly with Memostim.

During the objective study at the beginning of the course of treatment, diffuse organic symptoms in combination with focal syndromes were determined in all patients. Oculomotor disorders prevailed such as: convergence weakness, restriction of the view upwards, insufficiency of abductor nerves. Asymmetry of the facial muscles, nystagmus, impaired statics and coordination, and motor (varying degrees of severity), sensitive and tonic disorders have been reported. Indirect signs of cerebrospinal fluid hypertension have been reported: decreased corneal reflexes, soreness of the eyeballs when pressed, the tongue swelling with visually pronounced impressions of teeth on the lateral surface.

The analysis of objective and subjective neurological symptoms allowed to distinguish the leading clinical syndromes in the examined patients: cephalic (93.3%), vestibulo-atactic (83.3%), cerebrospinal fluid (56.7%), asthenic (86.7%) and cognitive impairment syndrome (96.7%). Cephalgic syndrome was characterized by the severity, monotony headache, sometimes only in one half of the head, but more often - without a clear localization. The vestibulo-atactic syndrome was characterized by dizziness, shakiness when walking, which was intensified when looking at moving objects, and when changing body position, accompanied by impaired statics and coordination, and ataxia in the Romberg test. Cerebrospinal hypertension syndrome was characterized by a typical squeezing headache, with a feeling of pressure on the eyeballs and nausea, which led to increased neurological symptoms of secondary stem nature - oculomotor disorders, pyramidal signs, pathological reflexes, pseudobulbar disorders. Asthenic syndrome was a component of physical and mental fatigue. Cognitive impairment of varying severity was detected in almost all examined patients. In patients of the comparison group, the frequency of these syndromes did not differ from that in patients of the main group.

After 3 months of using Memostim, the clinical picture in patients of the main group changed, in contrast to patients who did not receive phytocomplex (Table 3).

Table 3. Dynamics of clinical syndromes before and after the use of phytocomplex Memostim in the main group and after 3 months in the comparison group

Clinical syndromes	Main group (n=30)				Comparison group (n=30)				φ_1	φ_2
	Before using Memostim		After using Memostim		Basic data		After 3 month of treatment			
	abs.	%	abs.	%	abs.	%	abs.	%		
Cephalgic	28	93.3	18	60	26	85.0	28	93.3	3.281*	0.872
Vestibulo-atactic	25	83.3	14	46.6	23	76.7	22	73.3	3.085*	0.298
Cerebrospinal fluid hypertension	17	56.7	12	40	16	53.3	19	63.3	1.298	0.787
Asthenic	26	86.7	10	33.3	25	83.3	24	80.0	4.504*	0.334
Cognitive	29	96.7	20	66	27	90	26	86.7	3.345*	0.403

Note: * – $\varphi \geq 1.65$

After the use of Memostim, the prevalence of asthenic syndrome and cognitive impairment syndrome has decreased most significantly. This indicates the greatest effectiveness of the phytocomplex in the correction of these syndromes. Less positive dynamics was observed in the reduction of cephalic, vestibulo-atactic and cerebrospinal fluid-hypertension syndromes. In patients of the comparison group the frequency of cephalic syndrome has increased at the end of treatment.

To assess the state of cognitive functions in the examined patients, MoCA scale (Montreal Cognitive Assessment) was used. It is considered to be more sensitive to the detection of mild and moderate neurocognitive disorders.

The obtained data of testing on MoCA scale (Table 4) have shown that in the structure of neurocognitive functions in patients of both the main group and the comparison group in general, disturbances of optical-spatial activity prevailed (3.5 ± 1.9 and 3.5 ± 2.0 points, respectively), random attention (4.6 ± 3.0 and 4.5 ± 2.3 points, respectively), orientation 5.4 ± 1.9 and 5.4 ± 2.1 points), language (1.8 ± 1.0 and 1.7 ± 1.0 points) and abstract thinking (3.9 ± 1.8 and 4.0 ± 2.0 points).

The results of a study conducted at the end of Memostim course have shown that patients in the main group showed positive dynamics in the following parameters: optical-spatial activity, voluntary attention, memory, orientation and speech. The overall score on MoSA scale has increased by 2.7 points and amounted to 24.5 ± 1.4 points. In patients of the comparison group, total points on MoSA scale after three months of treatment has not changed significantly.

As a result of the conducted researches the corrective character of the effect of Memostim on NCD in patients with DE with signs of MS was established.

Table 4. The results of the study of neurocognitive functions on MoSA scale in patients with II stage DE with MS of the main group and comparison group (in points)

Scale parameter	Main group (n=30)		Comparison group (n=30)		P_1	P_2
	Before using Memostim	After using Memostim	Basic data	After 3 month of treatment		
Optical-spatial activity (executive function)	3,5 ± 1,9	3,7 ± 2,1*	3,5 ± 2,0	3,3 ± 2,1*	0,054	0,054
Naming objects	2,4 ± 2,0	2,6 ± 2,1*	2,5 ± 1,3	2,4 ± 1,0	0,054	0,048
Attention	4,6 ± 3,0	4,9 ± 2,8*	4,5 ± 2,3	4,3 ± 2,1*	0,058	0,051
Speech	1,8 ± 1,0	2,0 ± 1,3*	1,7 ± 1,0	1,6 ± 0,9*	0,052	0,058
Abstract thinking	3,9 ± 1,8	4,1 ± 2,1*	4,0 ± 2,0	3,8 ± 1,8*	0,057	0,058
Orientation	5,4 ± 1,9	5,6 ± 2,1*	5,4 ± 2,1	5,2 ± 1,8*	0,056	0,057
Total points	21,8 ± 7,1	22,6 ± 8,3*	21,6 ± 8,3	20,8 ± 7,6*	0,058	0,056

Note: * – $p < 0.05$

The "Frontal assessment battery" test was used to more accurately assess the presence of NCDs associated with frontal or subcortical cerebral dysfunction. The results of the assessment of the conceptualization function, speech rate, dynamic praxis, simple and complex choice reaction, the study of grasping reflexes are shown in table 5.

After using Memostim, the overall score on the FAB scale in the main group has increased by 1.1 points and amounted to 14.1 ± 8.6 points. For all parameters of the scale there was an increase in the number of points. In patients of the comparison group, the overall parameter on the FAB scale after three months of treatment has not changed significantly.

Table 5. The structure of cognitive impairment according to the FAB scale in the examined patients

Scale parameter	Main group (n=30)		Comparison group (n=30)		P_1	P_2
	Before using Memostim	After using Memostim	Basic data	After 3 month of treatment		
Total (max 18)	13,0 ± 7,8	14,1 ± 8,6*	13,7 ± 3,2	13,6 ± 2,8*	0,054	0,056

Conceptualization (max 3)	2,1 ± 1,9	2,3 ± 2,0*	2,3 ± 1,3	2,2 ± 0,8*	0,057	0,052
Speech rate (max 3)	1,9 ± 0,9	2,0 ± 1,0*	2,1 ± 0,9	2,0 ± 1,2*	0,058	0,053
Dynamic praxis (max 3)	2,2 ± 1,9	2,4 ± 1,7*	2,2 ± 1,0	2,3 ± 1,3*	0,058	0,048
Simple reaction of choice (max 3)	2,3 ± 0,8	2,4 ± 1,1*	2,4 ± 1,0	2,5 ± 1,3*	0,058	0,048
Complicated choice reaction (max 3)	2,2 ± 1,3	2,5 ± 1,6*	2,2 ± 0,8	2,3 ± 1,1*	0,057	0,058
Grasping reflex (max 3)	2,3 ± 1,8	2,5 ± 1,9*	2,4 ± 1,0	2,3 ± 1,2*	0,054	0,051

Note: * – $p < 0.05$

The examined patients mostly had emotional and volitional disorders, for the objectification of which the Beck and Spielberger scales were used (Table 6).

Analysis of these data indicates the presence of depression and anxiety in patients of both the main group and the comparison group.

After the course of Memostim, the number of points on the Beck scale has decreased by 1.4 points and the level of personal anxiety - by 13.5 points, situational - by 11.5 points. Thus, the use of Memostim had a positive effect on psycho-emotional disorders in patients with DE caused by MS.

Assessment of quality of life is considered as an integral characteristic of physical, mental and social functioning of a healthy and sick person. It is a very important component, in particular for assessing the effectiveness of treatment of patients. That is why in our study we studied the parameters of quality of life using the WHO quality of life questionnaire (WHOQOL-BREF).

All obtained parameters were within the average interval, which reflects the relative satisfaction / dissatisfaction of respondents with the overall quality of their lives. The highest parameters within the interval were obtained on the scale "Psychological health", i.e. psychological comfort, meaningfulness and emotional content of life, satisfaction with oneself and one's appearance, etc., are satisfactory according to the respondents. Physical health was rated slightly lower, meaning that patients complained of pain, sleep disturbances, lack of energy for work or daily activities, and inability to meet medical care needs. The lowest patients with DE rated the parameters on the scale "Environment", i.e. the actual financial situation, the ability to meet the needs of medical services, recreation, transport, etc., as well as the scale "Social Relations" - satisfaction with the level of social support and personal relationships.

After using Memostim in patients of the main group, feelings of psychological comfort and confidence, the level of satisfaction with themselves and their own lives have increased ("Psychological health"). Manifestations of emotional liability, exhaustion and sleep disturbances, decreased pain have decreased. The need for medical care remains relevant, but the energy for daily activities ("Physical Health") has increased, as well as the range and quality of social and personal functioning, satisfaction with communication and the level of support from loved ones ("Social Relations"). The assessment on the scale "Environment" has remained the lowest, i.e. the least patients were satisfied with their own financial situation, inability to meet the needs for medical services, recreation and other.

Table 6. The results of the study of the emotional state in the examined patients (in points)

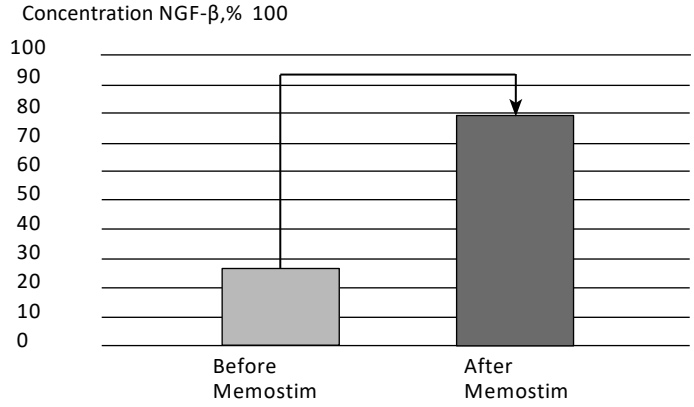
Parameter	Main group (n=30)		Comparison group (n=30)	
	Before using Memostim	After using Memostim	Basic data	After 3 month of treatment
Depression level on the Beck scale	13,4 ± 4,10	12,0 ± 1,80	13,7 ± 2,00	13,6 ± 1,80
The level of personal anxiety on the Spielberger scale	62,6 ± 5,62	49,1 ± 5,80	63,4 ± 6,70	63,0 ± 6,26
The level of situational anxiety on the Spielberger scale	43,8 ± 8,10	32,3 ± 7,60	43,8 ± 4,90	44,1 ± 5,64

Restriction of perfusion and hypoxia of brain tissues can lead to inhibition of the synthesis of neurotrophic growth factors (cerebral, glial, neurotrophic, nerve growth factor, etc.). Their deficiency reduces neuroplasticity - the ability of the nervous system to optimal structural adjustment in response to endogenous and exogenous stimuli. Neurotrophin deficiency promotes the development of apoptosis of neuronal structures, which is the main mechanism of nerve cell death in DE [19].

In recent years, much attention has been paid to nerve growth factor β (NGF-β), which is essential for the survival and development of sympathetic and sensory neurons in the peripheral nervous system, as well as cholinergic neurons in the CNS. In addition, NGF-β modulates the secretion of mediators (acetylcholine, glutamate, etc.) in the neuromuscular synapses and synaptosomes of hippocampus. NGF-β accelerates the growth of axons: studies have shown that it promotes their branching and elongation. NGF-β binds to two classes of receptors: the low-affinity nervous system growth receptor (LNGFR) and the neurotrophic tyrosine kinase receptor (TrkA). Decreased serum NGF-β is associated with severe neurological deficits and decreased cognitive function, and the presence of insulin resistance or diabetes only exacerbates pathological changes [19].

Therefore, to assess the effectiveness of Memostim in our study, we determined the concentration of NGF-β in the serum of patients.

A three-month course of Memostim in patients of the main group helped to normalize the restoration of the effectiveness of the regulatory function of NGF-β by 67% (Figure).



Effect of Memostim on NGF-β

The obtained results on the effect of the studied phytocomplex on NGF-β, in our opinion, are related to the ability of Memostim components to restore the main functions of neurotrophins associated with the ability to reduce oxidative stress and apoptosis by normalizing neurogenesis and forming progenitor (stem) neuronal cells - precursors of new functional neurons.

Tolerability and compliance studies with Memostim were analyzed by investigators who recorded the course of clinical symptoms during the follow-up period. They monitored comparability with background therapy, assessed the need for dose adjustment, and recorded the dynamics of condition and tolerability of Memostim in a specialized diary based on subjective observation of patients.

Total compliance was evaluated by the set of observations – as the average result for three months of observation and was calculated by the formula: Compliance = (100 * A / C * B) * 100%, where A is the number of doses taken, B is the number of days taken, C - number of intakes during the day. According to the results of the study, the total compliance in the group was 98%, which demonstrates a very high level of adherence of patients to the doctor's recommendations and overall good tolerability of Memostim. Comparability with background therapy (mainly antihypertensive drugs) was very good and did not require any adjustment of the dosing regimen or discontinuation of further Memostim use.

Among the adverse events, three days recurrent bowel movements disturbances requiring no interruption or dose adjustment were reported in two patients at the start of administration. One patient had recurrent dyspepsia and loss of appetite during the second week (the patient did not require any drug treatment and discontinuation of non-adjusted course of Memostim). Patients mainly paid attention to the general improvement of the condition and quality of life, increase of emotional level and physical activity (Table 7). No other adverse events or allergic reactions were observed in any of the patients during the follow-up.

Table 7. Assessment of the effectiveness and tolerance of Memostim course

Assessment	Efficiency		Tolerability	
	As per patient's assessment	As per doctor's assessment	As per patient's assessment	As per doctor's assessment
Very good	13	22	18	17
Good	13	7	10	11
Satisfactory	4	1	2	2
Unsatisfactory	0	0	0	0

Therefore, the results of the study allow us to draw the following conclusions.

Memostim has shown its effectiveness in patients with stage II DE caused by MS. The reception of Memostim for 3 months on the background of a standard course of therapy has contributed to a significant reduction in the main subjective and objective manifestations of DE. In most patients, the number of complaints has decreased. In a large number of patients there were a complete reduction of the subjective manifestations of the disease and increase of the subjective assessment of patients of certain parameters of their quality of life.

After a course of Memostim in patients with II stage DE, a positive dynamics in the neurocognitive sphere, namely the improvement of mnestic parameters and characteristics of voluntary attention, voluntary regulatory support and increase the effectiveness of mental activity in general were reported.

The positive effect of the phytocomplex on the psycho-emotional state of patients on the Beck's depression and Spielberger's anxiety scales was established. There was a decrease in emotional and affective disorders in the form of stabilization of mood, and reduction of anxiety and depressive disorders as well.

The three-month course of Memostim caused a normalizing effect in the examined patients, namely: an increase in the concentration of NGF-β in the serum by 67%, which indicates the restoration of neuroplasticity.

Analysis of the obtained data suggests that Memostim is a pathogenetically sound component of the complex therapy of patients with DE with MS and can be recommended for use in general clinical practice.

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