



UDC: 616-008.8-097:612.824.4

DOI: 10.18413/2313-8971-2016-2-2-99-106

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**PHARMACOLOGICAL MANAGEMENT OF IMMUNE AND OXIDATIVE
DISTURBANCES IN PATIENTS WITH ENCEPHALOPATHY
ON THE BACKGROUND OF HYPERTENSION**

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Abstract. Prior to treatment in patients with discirculatory encephalopathy stage II affected by hypertensive disease set at the system level elevation of proinflammatory and regulatory cytokines, stable metabolites of nitric oxide, a decrease of immunoglobulins M, G, A, disbalance of the complement system components, development oxidative stress. Inclusion of a comprehensive drug treatment of patients with discirculatory encephalopathy cerebrolysin combination with meksidol normalizes the concentration of C₃ and C₄ components of the complement system, IgG, malondialdehyde, catalase activity, total antioxidant activity of blood serum, corrects, but not to the level of standards, the contents of cytokines (TNF, IL-1 β , IL-6, IL-8, IL-18, IF γ , IL-2, IL-17), complement component C₅, IgA, acylhydroperoxide, neopterin and increases anti-inflammatory cytokines. Using emoxipine and piracetam as part of pharmacotherapy vascular encephalopathy stage II, compared with a combination of cerebrolysin and meksidol to further normalize levels of IL-17, C-reactive protein, increasingly closer to that of a control group of IL-6, IL-2 IL-18, C₅, C_{5a} component of complement, IgM, AGP, SM_{NO}, increases the concentration of the complement system and cytokine network controllers. Included in the complex pharmacotherapy of patients with discirculatory encephalopathy and a combination aktovegin and cereton has maximum efficiency, normalizing 52% and 48% broken correlation immune parameters.

Keywords: immune, oxidant disturbances, discirculatory encephalopathy, cerebrolysin, meksidol, emoxipine, piracetam, aktovegin, cereton

Introduction. Modern Angiology is characterized by the increasing number of patients with cerebrovascular disorders as a result of population aging. Along with acute forms of cerebrovascular diseases, chronic brain ischemia is making a significant contribution to the high morbidity and mortality of the population [1, 2]. The Russian Ministry of Health Order "On approval of the scientific medical science platforms" (№ 281 dated 30.04.2013) indicated on the high mortality rate of working-age persons from diseases of the circulatory system, which has a negative impact on demographics, medical and social and economic development of the country.

Chronic brain ischemia, also referred as encephalopathy, is a syndrome which slowly progressive brain dysfunction with cognitive and

other neurological defects, developing as a result of diffuse and / or fine-focal brain damage tissue under conditions of permanent failure of its blood supply or recurrent acute disorders. DEP is a heterogeneous syndrome etiopathogenesis, and in its appearance it plays a role of immune mechanisms, metabolic disorders along with hemorheological defects and endothelial dysfunction [3, 4, 5, 6].

Encephalopathy which is caused by arterial hypertension, activates microgliaocyte resulting in the induction of a local inflammatory response involving cytokines. The important target cells for the last astrocytes are involved in decreasing immune tolerance of the organism to the brain tissues, together with the processes of apoptosis and endothelial dysfunction resulting in damage to neuronal tissue. Immune inflammation and lipid

metabolism lead to irreversible damage to the membrane phospholipid complexes and destructive processes in the glia, which is one of the reasons for the clinical manifestations of DEP [7, 8, 9, 10, 11].

It should be appreciated that cytokines, complement system and immunoglobulins are the most important and versatile functionally group of humoral immune status factors involved in mediating endothelial functions realizing intercellular interactions during hematopoiesis, inflammation, immune processes and intersystem communications [12, 13].

A study on the state of the immune and oxidative status and correction of such violations are relevant [14, 15, 16].

These works provide an opportunity to create new methods of early diagnosis and personalized treatment approach based on the identified neuroendocrine and immune mechanisms of cerebrovascular diseases.

So, the development of pathogenetically substantiated pharmacotherapeutic strategy of acute and chronic ischemic brain damage is one of the urgent problems of modern medicine.

Research objective is to evaluate the clinical and laboratory efficiency combined using drugs with nootropic and antioxidant activity in patients with discirculatory encephalopathy affected by hypertensive disease.

OWN RESEARCHES

Clinical impressions. The investigations were carried out establishing of the neurological department of BMU «Kursk regional clinical hospital» at the Department of Neurology and Neurosurgery of the Kursk State Medical University. In the placebo-uncontrolled survey there were 48 patients with stage II DEP affected by essential hypertensive disease grade 2, stage 2, the risk 2 (active treatment group) and 12 healthy patients (comparison group). The age of patients and members of the active treatment group was 50 ± 5 years. The diagnosis was explained by the results of preassessment: 1) the availability of health disorders, including cognitive and psycho-emotional spheres; 2) presence of neurological syndromes - vestibulo-ataxic syndrome, hereditary cerebellar ataxia, pyramid sign, pseudobulbar syndrome; 3) the presence of cognitive dysfunction syndrome; 4) vascular pattern of changes in the brain by MRT in the form of leukoaraiosis, lacunar focus inside of mild and moderate hydrocephalus.

Inclusion criteria into the active treatment group: female, DEP stage II affected by hypertensive disease

grade 2, stage 2, the risk is 2, diagnosed 5 or more years ago, in accordance with the recommendations of the World Health Organization and the International Society of Hypertension (WHO/ISH, 1999), having a regular menstrual cycle, tolerability profile, written consent to participate in the research. Exclusionary criteria was haemodynamic stenoses of the brachiocephalic and cerebral vascular disorders, rhythm disturbance of heart function, heart disease, myocardial infarction, postinfarction cardiosclerosis and cardiac angina or the presence of indications of their anamnesis, secondary hypertension, congestive heart failure, diabetes or impaired glucose tolerance, expressed or moderate atherosclerotic changes in retinal vessels, carried over serious head injuries, alcoholism, apoplectic attack in past medical history, with an estimate of the Khachinsky's scale less than 7 points, severe and the most severe condition, somatic pathology in the stage of incomplete remission or exacerbation, allergic reactions to treatment, refusal of treatment.

Examination technic included a clinical evaluation of neurological status, the investigation of cognitive functions on a scale «MMSE», the severity of cognitive impairment on a scale general deterioration – Global Deterioration Rating. To confirm the vascular temperament of the DEP and the extent of brain damage using MRT (Philips company unit, the magnetic field voltage of 1 Tesla). All patients were counseled by an ophthalmologist and a cardiologist.

Patients with DEP were accidentally divided into three groups of 16 people; they received 10-day drug treatment with various combinations of nootropic and antioxidant drugs during two weeks of comprehensive basic.

The daily basic pharmacotherapy there were included angiotensin-converting enzyme inhibitor enalapril (Hemofarm AD, Serbia) to 10 mg per day in and ethyl apovincaminic acid (Bravinton, vinpocetine, Vintsetin, Cavintonum of «Gedeon Richter», Hungary) 25 mg 500.0 ml of a 0.9% NaCl solution intravenously. Additional pharmacotherapy it was conducted by paired combinations of drugs with neurometabolic action with antioxidant and antihypoxic effects, daily for 10 days. Their application corresponds to the recommendations of the Russian management of patients with chronic cerebral ischemia and Federal guidelines on using of medicines.

Patients in Group 1 were administered every day 2152 mg concentrate cerebrolysin (set of peptides derived from pig's brain) (Cere, «EBEWE Pharma Ges.mbH Nfg. KG», Austria) intravenously in 100.0

ml of 0.9% solution sodium chloride, and 2-ethyl-6-methyl-3-hydroxypyridine succinate (Mexidol, LLC «NPK Pharmasoft», Russia), 5 mL of the solution intravenously. Patients in Group 2 were received once a day 40 mg of 3-hydroxy-6-methyl-2-ethylpyridine (Emoksipin, endocrine Plant, Moscow, Russia) as a 4% solution of 1 ml intramuscularly and 1000 mg of 2-oxo-1 pyrrolidine-acetamide (Piracetam, Borisov factory, Belarus) in the form of 5 ml of 20% solution intravenously. In the 3rd group it was once daily administered 200 mg aktovegina (Aktovegin, «Nycomed Austria GmbH», Austria) in a 5 mL containing 200 mg aktovegina, intravenously and 1000 mg of choline alfostserata (Cereton, «Sotex FarmFirma», Russia) intravenously in 200.0 ml of 0.9% sodium chloride solution.

Treatment was in line with the principles of evidence-based medicine. All the patients were on the nitrate-free diet.

Laboratory assessment. To determine the laboratory parameters of blood from the cubital vein was taken in the morning on an empty stomach, in the first day of admission and before discharge on the 14th day in a volume of 10 ml.

In making an assessment of haemogram it has been based upon the physiological norm, corresponding to the international system of units in clinical investigations.

Determination of levels of TNF, IL-1 β , IL-6, IL-8, IL-18, IL-4, IL-10 receptor antagonist IL-1 (IL-1 Ra), INF γ , IL-2, IL-17, complement components (C₃, C_{3a}, C₄, C₅, C_{5a}), its inhibitors (factor H, C₁-inhibitor), immunoglobulin class M, G, A (IgM, G, A), ceruloplasmin, and neopterin C-reactive protein was performed with the help of commercial panel of immunoferment analysis with detection of the products in the wavelength range 405-630 nm. C1 inhibitor concentration was determined by a chromogenic method ability to inhibit C1 esterase.

The intensity of the LPO processes were evaluated by conventional methods on the content in the blood plasma polyunsaturated fatty acid degradation products - derivatives of thiobarbituric acid (MDA and AGP). Catalase activity was determined [19] and superoxide dismutase [18]. Total plasma antioxidant activity was determined by a method of inhibition of the oxidation of ascorbate and ferroevoke corrosion Tween-80 and MDA. Absorbance was measured at 532 nm after 48 hours of incubation at 40 ° C. The content of the stable metabolite of nitric oxide in the blood plasma was determined spectrophotometrically using the Griess reagent and detection appeared products at a wavelength of 540 nm. The results were calculated by standard curve using solutions of sodium nitrite.

Analysis of clinical and laboratory results were carried out before and 2 weeks after the complex treatment of patients prior to discharge from office. The results of clinical, neuropsychological and laboratory tests were compared immune to the dynamics of treatment and with the same results it was in the active group.

Statistical analysis of the results. The clinical efficacy of the treatment was evaluated in points. The basis of the developed evaluation system is based on a retrospective analysis of 545 case histories of patients diagnosed with DEP, were hospitalized from 2009 to 2014 to assign points methodology consistent diagnostic procedure has been used for one to three a certain set of symptoms, which is based on sequential analysis method proposed by Wald. Clinical signs for building predictive tables were selected for the task. Then, for each criterion it was calculated probability of occurrence, and then calculate the smoothed particular characteristics in each of the studied sample population [19]. These values allow to calculate for each characteristic diagnostic factors and calculate the information content of each of the signs. Naturally there was another screening of non-informative features. In addition, for each chosen informative gradation characteristic of an indicator into three groups so as to equalize the diagnostic value of each indicator.

Statistical processing of the studying results was conducted according to generally accepted criteria variational-statistical analysis with the calculation of the average values (M), an error arithmetic mean (m) using the Microsoft Excel software package, 2010. Significant differences were evaluated by U-test. Correlation analysis was performed using Spearman's rank correlation coefficient. Differences were considered statistically significant with $p = 0,05$.

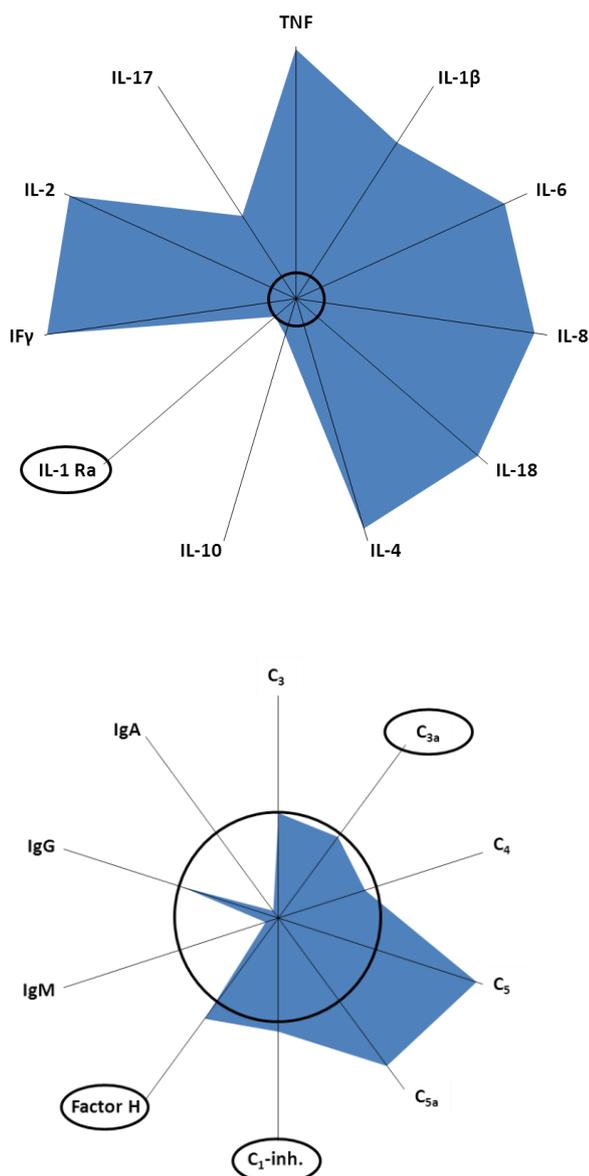
For immunological parameters were calculated ratio diagnostic value, determined by the formula of disorders of the immune system by selecting from all the studied parameters of the top three most distinguished level of standards expected level of immune disorders, ranking algorithm largest extent disorders conducted a correlation analysis between immune parameters and clinical results, calculates the sum of degrees of correction for each treatment regimen [20].

RESULTS OF RESEARCH

Changes in the immune and metabolic parameters in vascular encephalopathy affected by hypertensive disease. Indicators DEP patients with stage II affected by hypertensive disease in the target groups to treat each other don't differ. It was evaluated average, determined by the total in three groups. Prior to treatment in the patients' plasma DEP II stage essential hypertension found a

significant increase in the concentration of cytokines $INF\gamma$, IL-2, IL-17, anti-inflammatory (TNF, IL-1 β , IL-6, IL-8, IL-18) with simultaneous increase of anti-inflammatory IL-4 and IL-10, with unchanged content IL-1 Ra (fig. 1).

The detected increase in C_5 , C_{5a} , reduction of C_3 and C_4 components of the complement system and all studied classes of immunoglobulins (IgM, IgG, IgA) in unmodified concentration, compared to donors, inhibitors of the complement system (factor H, C_1 -inhibitor) and $C3a$ component (fig. 1).



Designations:

- 1 - the radius of the circle marked in the controls;
- 2 - - DEP indicators of patients with stage II affected by hypertensive disease;
- 3 - - $p > 0.05$, the rate of patients with stage II DEP affected by hypertensive disease isn't different from the comparison group.

Figure 1. Changes in immune parameters in patients with discirculatory encephalopathy stage II affected by hypertensive disease before treatment.

The blood plasma of patients DEP stage II found an increase in the concentration of the intermediate and final products of lipid peroxidation (MDA AGP) concentration SM_{NO} and CRP, a significant change in the antioxidant defense indicators (reduction of catalase activity, TAA serum CP level, increase of neopterin).

Pharmacological rehabilitation of patients with discirculatory encephalopathy against the background of essential hypertension drug combination with nootropic and antioxidant properties. Introduction to the treatment regimen of patients with DEP stage II affected by hypertensive disease cerebrolysin and mexidol normalized levels of C_3 , C_4 complement components and of IgG, to reduce the concentration of TNF, IL-1 β , IL-6, IL-8, IL-18, $INF\gamma$, IL-2, IL-17 C_5 complement component, increased IgA content (but not to the level of provisions recorded in the comparison group) increased in comparison with the moment of admission to the clinic, the content of anti-inflammatory cytokines IL-10 and IL-1 Ra (table 1).

When using emoxipine and piracetam and the normalization of levels of IL-17, C_3 , and C_4 components of complement, and IgG, correction (change in direction, but not up to the level of control) content of TNF, IL-1 β , IL-6, IL-8, IL 18, $INF\gamma$, IL-2, C_5 , C_{5a} complement components, IgA and M, increasing the concentration of anti-inflammatory cytokines IL-4, IL-10 and IL-1 Ra, complement regulators (C_1 -inhibitor and factor H) compared with the original results (table 1).

The combination of an aktovegin and cereton was the most effective as normalized the content in plasma of IL-1 β , IL-6, IL-2, IL-17, C_3 , C_4 -components of a complement, IgG, more on to comparison with other schemes, correction concentration C_{5a} -component of a complement, IgM and I increased the level of anti-inflammatory cytokine (IL-4, IL-10), IL-1 Ra, complement regulators (C_1 -inhibitor and factor H) (table 1).

Table 1

Change in the concentration of cytokines and complement system components in patients with stage II DEP affected by hypertensive disease in the application of neuroprotective combinations and antioxidant drugs (M±m; n=48)

Indicators	Units measurement s	1	2	3	4	5
		Control group	Patients with DEP stage II			
			Before treatment	Cerebrolysin and Mexidol	Emoxipine and Piracetam	Aktovegin and Cereton
TNF	pg/ml	0,5±0,07	20,23±0,91 ^{*1}	10,12±1,05 ^{*1,2}	9,07±0,46 ^{*1,2}	9,1±0,53 ^{*1,2}
IL-1β	pg/ml	1,6±0,09	11,79±0,84 ^{*1}	6,22±0,43 ^{*1,2}	6,26±0,48 ^{*1,2}	1,29±0,14 ^{*2,4}
IL-6	pg/ml	1,9±0,05	17,2±1,08 ^{*1}	5,32±0,51 ^{*1,2}	4,06±0,41 ^{*1,3}	2,34±0,42 ^{*2,4}
IL-8	pg/ml	2,0±0,11	26,38±1,88 ^{*1}	6,39±0,58 ^{*1,2}	5,76±0,94 ^{*1,2}	7,0±0,55 ^{*1,2}
IL-18	pg/ml	50,1±2,3	1539,4±137,1 ^{*1}	677,5±38,4 ^{*1,2}	288,1±20,1 ^{*1,3}	610,4±66,3 ^{*1,2,4}
IL-4	pg/ml	0,3±0,02	7,53±0,67 ^{*1}	6,4±0,41 ^{*1}	11,76±0,62 ^{*1,3}	11,18±0,68 ^{*1,3}
IL-10	pg/ml	2,5±0,08	3,07±0,2 ^{*1}	11,56±0,54 ^{*1,2}	12,98±0,51 ^{*1,2}	13,47±0,41 ^{*1,2}
IL-1 Ra	pg/ml	131,4±12,7	142,7±13,5	159,2±10,1 ^{*1}	200,3±21,8 ^{*1,3}	197,2±10,7 ^{*1,3}
IFγ	pg/ml	0,3±0,01	288,94±1,54 ^{*1}	65,12±3,76 ^{*1,2}	45,65±3,57 ^{*1,3}	68,84±8,5 ^{*1,2,4}
IL-2	pg/ml	0,2±0,03	12,54±0,31 ^{*1}	6,64±0,43 ^{*1,2}	1,5±0,09 ^{*1,3}	1,81±0,12 ^{*1,3}
IL-17	pg/ml	6,31±0,8	24,65±1,95 ^{*1}	10,75±1,25 ^{*1,2}	5,58±0,42 ^{*2,3}	5,54±0,5 ^{*2,3}
C ₃	mg/dl	127,9±4,68	119,92±2,83 ^{*1}	133,83±3,64 ^{*2}	135,5±3,32 ^{*2}	135,4±2,9 ^{*2}
C _{3a}	ng/ml	49,4±5,6	44,2±2,7	50,6±6,07	47,9±5,54	45,13±5,09
C ₄	mg/dl	25,8±2,52	20,78±0,96 ^{*1}	26,92±1,29 ^{*2}	28,1±1,05 ^{*2}	27,0±1,34 ^{*2}
C ₅	ng/ml	108,6±9,1	200,3±10,1 ^{*1}	174,2±8,91 ^{*1,2}	131,2±10,3 ^{*1,3}	144,3±8,0 ^{*1,3}
C _{5a}	ng/ml	81,8±5,24	133,4±6,2 ^{*1}	124,8±5,5 ^{*1}	100,6±8,82 ^{*1,3}	98,3±4,7 ^{*1,3}
C _{1-inh.}	ng/ml	386,3±17,9	391,5±20,4	407,8±18,1	587,2±48,8 ^{*1,3}	713,4±61,2 ^{*1,4}
Factor H	ng/ml	38,1±8,3	42,3±6,33	44,5±5,3	62,7±7,1 ^{*1,3}	68,16±7,9 ^{*1,3}
IgM	mg/dl	80,8±4,8	9,69±1,42 ^{*1}	8,33±0,51 ^{*1}	12,36±0,94 ^{*1,3}	34,88±2,34 ^{*1,4}
IgG	mg/dl	1284,6±39,2	1148,19±25,3 ^{*1}	1222,0±31,1 ^{*2}	1214,8±33,84 ^{*2}	1352,5±55,34 ^{*2}
IgA	mg/dl	44,9±6,8	3,61±0,31 ^{*1}	25,9±2,31 ^{*1,2}	23,13±2,33 ^{*1,2}	26,99±1,5 ^{*1,2}

Note. In the table there are marked with an asterisk significant differences of arithmetic means (p = 0,05); figures marked with an asterisk beside are with respect to which group indexes are given to these differences.

Comparison efficiency of clinical and laboratory pharmacological correction of immune and oxidant disturbances in vascular encephalopathy affected by hypertension. On admission to hospital in patients with stage II DEP set change 25 of 30 (83.3%) there was established immune metabolic indicators indicating the presence of oxidative stress in patients, immune inflammation and endothelial dysfunction (table 2).

Using combination therapy with combination of cerebrolysin meksidol was normalized 6 (24%) and corrected, but not to the performance standards 13

(52%) of the 25 modified before treatment the amount of immune and oxidative parameters. Using emoxipine and piracetam normalized 7 (28%) and 18 to correct (72%), laboratory parameters. The most effective, according to the dynamics of change in the treatment of laboratory result, has a combination of aktovegin and cereton since the introduction of these products into the complex pharmacotherapy patients DEP stage II normalized 12 of 25 (48%) and to correct the 13 (52%) changed at the beginning of treatment immune parameters (table 2).

Table 2

Immune efficacy of combinations neuroprotective and antioxidant drugs in patients with DEP (M±m; n=48)

№	Patient group	Changed laboratory indicators before treatment	Therefrom (%):		
			Corrected	Normalized	Without changing
1.	Cerebrolysin +meksidol	83,3%	52,0	24,0	24,0
2.	Emoksipin +piracetam		72,0	28,0	0
3.	Aktovegin +cereton		52,0	48,0	0

By proportion of the number of violations of lab values in patients with different pharmacotherapy with the division of powers of the depth disorders found that before treatment 25 out of 30 it studied indicators which were violated in varying degrees. Since level disturbances (LD) III it was 17 indicators with LD II - 3, and a LD I - 5, wherein the formula of disturbances (FD) were: $IF\gamma^+_3$, MDA^+_3 , TNF^+_3 . After the treatment, which included a combination of cerebrolysin and mexidol, the reduce of a number modified indicators was to 19, with a LD III turned 10 indicators with LD II - 8, with the I LD - 1 and FD consisted of $IFN\gamma^+_3$, $IL-2^+_3$, TNF^+_3 .

After inclusion complex of emoxipine pharmacotherapy and piracetam there were 18 disturbed indicators, it was 9 LD with III, II and I, 5 and 4 score, FD was $IFN\gamma^+_3$, $IL-4^+_3$, TNF^+_3 . The most effective was the use of a combination aktovegina and cereton since reduced the number of indicators broken to 13, while LD was 8 with the III, II and I, respectively 2 and 3. FD comprised $IF\gamma^+_3$, $IL-4^+_3$, TNF^+_3 .

In accordance with the sum of the degrees of correction for each treatment regimen it was found that correction of Immune Parameters in Patients DEP stage II affected by hypertensive disease, a combination of aktovegina and cereton was more effective with as a sum of compensation levels for the scheme was 5540, with the combination emoxipine and piracetam amount correction degree was 3497,

while the combined using of cerebrolysin and mexidol amount of compensation was 127 degrees.

There was a coincidence when comparing the changes in the immune status and metabolic parameters under the influence of the various schemes of pharmacotherapy with clinical result.

So, using cerebrolysin and mexidol reduced the mean scores of clinical symptoms with a $26,2 \pm 0,9$ to $23,3 \pm 0,7$ ($p = 0,05$), and using emoxipine piracetam to $19,1 \pm 1,7$ ($p = 0.05$). There was a reduction decrease in egocentric symptoms of the disease as a result of treatment, evidence reduction of anisoreflexia, mend of cognitive function and emotional state of patients.

The research results have shown the most maximal clinical efficacy has a therapeutic regimen including aktovegin and cereton, containing the number of points to $14,8 \pm 1,0$ ($p = 0,01$); in the treatment group it was showed a significant decrease in the intensity of complaints, a significant improvement in cognitive functions and emotional state of patients.

Based on experience it can be concluded that the most effective treatment is the combination of DEP aktovegina with cereton.

Through studies of laboratory correlations parameters, complaints and clinical syndromes in patients with discirculatory encephalopathy stage II affected by hypertensive disease there were positive things between the levels $IL-6$, $IL-17$ $IF\gamma$ and intensity of headaches, dizziness, sonitus, shaky

walk, defective memory and attention, mood swings, vestibular ataxia, hereditary cerebellar ataxia, pseudobulbar syndrome, pyramid sign, psychopathological symptom. Negative significant correlations were established between these symptoms and syndromes and neopterin content, activity of catalase.

Immune alterations are one of the stages of the ischemic cascade reaser hypoxia and it occurs of shifts ionic homeostasis, «the phenomenon of excitotoxicity», oxidative stress, which leads to the gradual degeneration and death of neurons [6, 21, 22]. Patients with DEP stage II affected by hypertensive disease before treatment there were established signs of oxidative stress (elevated levels of lipid peroxidation products and stable metabolites of nitric oxide, a decrease of antioxidant protection factor) and immune inflammation which level was rising especially of pro-inflammatory cytokines, imbalances of components complement system, reduction of immunoglobulins.

The combination of aktovegina cereton was effective in these circumstances because both activates cereton phosphatidylcholine synthesis - a major phospholipid membrane components, and stimulates the release of acetylcholine, - neurotransmitter synaptic transmission provides enhances metabolic processes and improves blood flow in the central nervous system. Aktovegin is an effective antioxidant and antihypoxant, it's also hemoderivative obtained by dialysis and ultrafiltration. Antioxidant effect of aktovegina is determining its neuroprotective effects, manifested in the reduction of reactive oxygen species, and this effect is dose-dependent. It has insulinoid effects of the drug, also a positive effect on the glucose transport and utilization, we cannot entirely possible that there are the presence of neurotrophic and anabolic effects on the central nervous system. Most of the drug's effectiveness is related to the rate of realization of its biological effects. More pronounced immune metabolic effects can be explained as a direct effect on the cells of the immune system by these pharmacodynamic effects caused by a decrease in the number of oxygen free radicals and reducing cellular antioxidant status systems [16, 23].

In a less degree a combination of piracetam and emoxipine was incompetent. Piracetam is a metabolite with strong nootropic effects and a complex membrane-stabilizing action emoxipin has antioxidant, antihypoxant properties, vasculoprotective and antiplatelet therapy. Probably these effects are not enough for complete relief of ischemic and oxidative processes in the brain to

normalize capillary endothelial function and energy processes in neurocytes.

The least effective was a combination of cerebrolysin and mexidol in the correction of immune and metabolic disorders with DEP, although the derivatives of 3-hydroxypyridine have marked antioxidant activity. We can assume that cerebrolysin, which provides metabolic regulation, neuroprotection, functional neuromodulation and neurotrophic activity in hypoxic conditions influence in less extent on pathogenetic mechanisms of DEP in comparison with piracetam and cereton [24, 25]. Suggests that effective approaches will be using L-arginine and arginase inhibitors [26, 27, 28].

So, based on the dynamics of immunological and oxidative parameters and regression of clinical symptoms of the disease can be argued that the degree of reducing the effectiveness of the investigated combination of medications nootropic and antioxidant action when DEP stage II affected by hypertensive disease are located in the following order: complex pharmacotherapy, including aktovegin with cereton → emoxipin with piracetam → cerebrolysin with meksidol.

DEP triggers to neurological deficits, cognitive disorders, threatens the development of stroke. Early treatment can save the professional, social and personal adaptation of the patient for many years, it improves the prognostication to the duration of the patient's life.

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