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Research Article

Disorders of the immune status in patients with chronic cerebral ischemia; differentiated pharmacological correction

Anastasiya A. Shulginova[1], Alexander I. Konoplya[1], Natalya A. Bystrova[1]

1 *Kursk State Medical University of the Ministry of Healthcare of Russia, 3 K. Marks St., Kursk 305041, Russian Federation*

Corresponding author: *Alexander I. Konoplya* (konoplya51@mail.ru)

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Abstract

Introduction: Chronic cerebral ischemia (CCI) accounts for 60-75% of all cerebrovascular diseases in Russia and around the world. **The problem:** the issues concerning the role of immunity in the pathogenesis of CCI depending on the main etiologic factor and stage of the disease are hardly elaborated, which makes the main pharmacological correction impossible. **The objective of the study** is to establish the immune disorder patterns in patients with CCI I-II associated with arterial hypertension and to develop differentiated pharmacological methods for their correction.

Material and methods: The results of treatment of 104 patients of Kursk Regional Clinical Hospital with CCI associated with II-stage arterial hypertension were analyzed: 52 patients were with CCI I stage (2^{th}-4^{th} groups of 12-14 patients) and 52 patients were with CCI II stage (5^{th}-7^{th} groups of 12-14 patients), aged 50±5, who received the basic pharmacological therapy (enalapril and vinpocetine). The patients of the 2^{nd} and 5^{th} groups additionally received ceraxon and mexicor, those of the 3^{rd} and the 6^{th} groups additionally received immunomodulator glutoxim, and those from the 4^{th} and 7^{th} groups received polyoxidonium. Twenty-two healthy donors were in the control group. Immune disorders were assessed by the parameters of the functional activity of neutrophils, levels of cytokines in plasma, components of the complement and inhibitors.

Results and discussion: In the case of CCI I and II stages similar proinflamatory immune disorders were detected, which is indicative of immune inflammation. The inclusion of glutoxime and polyoxidonium in a complex pharmacotherapy helps reduce the severity of immune and neuropsychic status indicators, which are more evident in case of stage II.

Conclusions: In case of CCI I stage, the medications used can be arranged according to their clinico-immunological efficacy in ascending order: ceraxon+mexicore ® ceraxon+mexicor+glutoxim ® ceraxon+mexicor+polyoxidonium, and in case of CCI II stage: ceraxon+mexicor ® ceraxon+mexicor+polyoxidonium = ceraxon+mexicor+glutoxim.

Keywords

chronic cerebral ischemia; neurological, cognitive, immune disorders; immunomodulating correction.

Introduction

At present, cerebrovascular diseases are viewed as some of the most pressing social and medical problems and even as an "epidemic of the XXI century". Late diagnosing, prophylaxis and treatment of vascular diseases can lead to disease progression and the development of severe dysfunctions of the brain, which in turn results in labor and social disadaptation of patients. Among the various neurological symptoms observed in this category of patients, of crucial importance are cognitive dysfunctions, as it is their appearance that largely determines a decrease in the quality of patients' life. According to their clinical manifestations, vascular cognitive disorders are quite heterogeneous, which can be explained, on the one hand, by different localization of brain damaged areas, and, on the other hand, by differences in developing cognitive deficit. Vascular cognitive disorders, including both dementia and non-dementia forms of cognitive decline, are observed in 2.8-10% of people over 65 years of age (Zakharova et al. 2014, Levin 2012, Litvinenko et al. 2013, Tanashyan et al. 2016, Wancata et al. 2016).

In Russia, as well as in the whole world, cerebrovascular diseases ranked second both in the structure of mortality caused by circulatory system diseases and in the overall mortality of the population, with chronic cerebral ischemia (CCI) accounting for 60-75% of all cerebrovascular diseases. Now people over 65 years of age make up to 10-15% of the population, and this figure is expected to reach 20-25% in 20 years, with the number of people over 80 to increase most rapidly, and their number in the next decade may increase 3 times. A strong trend of the last 10-15 years has also been that the contingent of patients with various types of cerebrovascular diseases has become much younger, which results from a constant increase in the impact of unfavorable external factors and low effectiveness of programs to prevent socially significant diseases, primarily atherosclerosis and arterial hypertension (AH) (Zakharova et al. 2014, Skvortsova et al. 2008, Kadykov et al. 2014, Mitra et al. 2011).

In the Russian literature, the following terms are most frequently used to refer to clinical signs of CCI: chronic cerebral circulatory insufficiency, dyscirculatory encephalopathy, chronic cerebrovascular disease, etc. All these are a variety of cerebral vascular pathology with a slowly progressing diffuse damage to the blood supply to the brain and increasing various functioning defects. CCI is clinically manifested by a complex of neurological and psychiatric syndromes, the most usual being such subjective manifestations as headache, dizziness, tinnitus, and fast fatigue. The core of the clinical picture that determines the severity of patients' condition is an increased limitation of cognitive and motor functions. Further cognitive impairment may develop into vascular dementia (Levin et al. 2014, Roman et al. 2002, Ovesgharan and Hachinski 2010). CCI is, on the one hand, a risk factor for stroke, and, on the other hand, is a cause of a gradual increase in neurological and psychiatric disorders, a slowly progressing damage to cerebral circulation of a multifocal or diffuse nature, resulting from the gradual accumulation of ischemic and secondary degenerative changes in the brain caused by recurrent ischemic episodes. The manifestations of this disease, depending on the stage of the process, can vary from subclinical phenomena to the signs of persistent neurological deficit combined with emotional-personal and cognitive disorders (O'Brien et al. 2003, Xu et al. 2004).

The main etiological factors leading to neurologic manifestations in CCI patients are determined by two factors: AH, cerebral atherosclerosis and their combination. In accordance with these views, several forms of CCI are distinguished: hypertonic form, which can manifest itself as sub-cortical arteriosclerotic encephalopathy and hypertensive multi-infarct encephalopathy; atherosclerotic form and mixed forms. Less common are CCI forms associated with other diseases (diabetes, metabolic syndrome, systemic diseases, anti-phospholipid syndrome, etc.) (Zakharova et al. 2014, Tanashyan et al. 2016, Gusev and Chukanova 2015, Roger et al. 2012).

In the pathogenesis of CCI formation, a crucial role is played by long-term cerebral hypoperfusion, due to local stenoses of cerebral arteries and other mechanical obstructions to the blood flow, micro- and macroangiopathy. Pathology of small cerebral arteries (cerebral microangiopathy), affecting primarily the longest penetrating medullary arteries of the cerebral hemispheres and brainstem. The main cause of cerebral microangiopathy is AH, less frequent causes of damage to small cerebral arteries being amyloid angiopathy, hereditary and inflammatory vasculopathies. Antemortem verification of small vascular lesions is not always possible, but their consequences – leukoencephalopathy, lacunar status, microinfarcts, micro-hemorrhaging, secondary cerebral atrophy, etc. – can be detected through neuroimaging (O'Brien et al. 2003, Gusev and Chukanova 2015, Zakharov et al. 2016, Pantoni et al. 2007, Cordonnier et al. 2006).

An cruicial role in the development of CCI is also played by the dysfunction of neurovascular units that unite neurons, astrocytes and cells of the vascular wall into a single functional system. The dysfunction of neurovascular units leads to the failure of cerebral autoregulation mechanisms, accompanied by the damage to the blood-brain barrier. One of the most important parts of this process is the development of oxidative stress and endothelial dysfunction in small vessels, which results in their decreased reactivity and a deficiency in perfusion of the functionally active areas of the brain (Gusev and Chukanova 2015, Girouard and Iadecola 2006, Farrall and Wardlaw 2009).

AH contributes both to the development and progression of CCI. There is increasing evidence that AH is the most powerful modifiable risk factor for developing cerebral vascular dysfunction and can result in a gradual decrease in cognitive functions (Gavrilyuk et al. 2016, Jellinger and Attems 2010, Nelson et al. 2011).

As is known, the nature of an immune response and patterns of pathophysiological changes in case of ische-

mic/hypoxic tissue disorders depend on preferential activation of subpopulations of T-lymphocytes, their synthesizing cytokines of various types and forming a "cytokine cascade", namely a ratio of pro-inflammatory and anti-inflammatory cytokines (Ketlinsky and Simbirtsev 2008). In recent years, an increasing number of facts have been accumulated about an important role of the immune system in cerebrovascular pathology, for example, in the pathogenesis of atherosclerosis and arterial hypertension, which are essential for emergence and progression of CCI, the key role is played by the immuno-inflammatory mechanisms. Cytokines of T-helper (Th1) lymphocytes – IL-2, IFNγ, as well as chemokines macrophage, especially MCP-1, are considered as pro-atherogenic, whereas cytokines Th2 (IL-4, IL-5, IL- 10, IL-13) play an anti-atherogenic role (Zurochka et al. 2013, Voronina et al. 2014). AH-induced chronic ischemization of brain tissues causes immune inflammation and lipid metabolism disorder, which leads to irreversible damage to phospholipid membrane complexes and a destructive process in neuroglia (Gavrilyuk et al. 2016, Kamchatnov et al. 2016, Menshikov et al. 2010).

Problem

In clinical practice, neurological and sometimes mental disorders reflecting brain dysfunction in senior patients, especially those suffering from cardiovascular diseases, are attributed to, which results in overdiagnosis the disease, which, in turn, leaves its diagnosis and treatment insufficiently developed and questions the effectiveness of some vasoactive drugs widely used in clinical practice. Moreover, to evaluate the effect of treating CCI, no modern clinical and psychometric research scales have been applied, and the diagnosis has never been verified by modern neuropsychological and neuroimaging methods (Gusev and Chukanova 2015, Zakharov et al. 2016).

The literature quite comprehensively covers the issues of the involvement of immune mechanisms in the onset and development of atherosclerosis, AH, acute forms of cerebrovascular pathology, but there are a number of open issues concerning the role of immunity in the pathogenesis of CCI, depending on the main etiologic factor and a stage of the disease, which prevents the relevant pathogenetic pharmacological correction (Gavrilyuk et al. 2016, Menshikov et al. 2010, Turmova et al. 2014, Tabeeva 2015, Libby et al. 2011).

Improving the understanding of the pathogenesis of CCI is of great importance for selecting the main directions for pharmacological correction of disorders. In accordance with this, apart from a vasotropic therapy, elimination of causes of microangiopathies (arterial hypertension, diabetes, etc.), correction of endothelial dysfunction, oxidative stress, provision of neuroprotection, on the agenda is the application of immunomodulators to correct immune disorders in the early stages of the disease (Zakharova et al. 2014, Skvortsova et al. 2008, Zurochka et al. 2013, Vorobyova et al. 2010).

It is logical to assume that detecting and correcting immune disorders in case of CCI of hypertensive origin may affect the severity of neurological symptoms. In this regard, studies on the state of the immune (the cytokine and complement system, immunoglobulins) and metabolic parameters (lipid peroxidation, antioxidant defense, stable metabolites of nitric oxide) are of relevance. This circumstance is also emphasized in the Order of the Ministry of Healthcare of Russia No. 281 of 30 April 2013 on the expediency of developing new methods for early diagnosis and a personified approach to the treatment based on studying neurohumoral and immune mechanisms of cardiovascular disease development.

Thus, the development of a pharmacological strategy for correcting immune system disorders in case of acute and chronic ischemic damage to the brain is one of the urgent problems of modern medicine.

Objective: to establish the patterns of immune disorders in patients with CCI I-II associated with arterial hypertension and to develop differentiated pharmacological methods for their correction.

Materials and methods

During 2014–2017 (retrospectively), under outpatient observation there were 120 patients with CCI associated with II-degree II-stage arterial hypertension risk 2, who received an antihypertensive therapy, including β-adrenoblockers, calcium antagonists, angiotensin-converting enzyme inhibitors, and diuretics.

The prospective study included 104 patients, of whom 76 female and 28 male patients made up the main group of those hospitalized in the neurological department of Kursk Regional Clinical Hospital with arterial pressure corrected to the target level, with CCI associated with hypertension, of whom 52 patients were with CCI I stage (1st main group) and 52 patients with CCI II stage (2nd main group) aged 50±5.

The patients were included into the study basing on informed consent and the decision of the regional ethics committee.

In addition, the clinical and laboratory indicators of 22 healthy donors (aged 52±2) that formed the control group 1 were studied; the obtained data are accepted as a conditional norm.

The criteria for including patients into the main group were: age from 40 to 60 years; absence of concomitant diseases in the acute stage, having CCI on the background of II-degree II-stage hypertension risk 2, which had been diagnosed 5 or more years ago in accordance with the recommendations of the World Health Organization and the International Society for Hypertension (ISH, 1999). The diagnosis of II-stage CCI is substantiated by a set of clinical and imaging symptoms: 1) impaired well-being; 2) organic cerebral focal symptoms in the form of vestibulo-atactic, cerebellar, pyramidal, pseudobulbar syndromes; 3) syndrome of cognitive dysfunction; 4) a vascular

profile of changes in the brain according to magnetic resonance imaging (MRI) in the form of leukoarose, lacunar foci, internal mild and moderate hydrocephalus.

Exclusion criteria were: hemodynamically significant stenoses of brachiocephalic and cerebral vessels, disturbances in the cardiac rhythm and conduction; heart defects; myocardial infarction, postinfarction cardiosclerosis and progressive angina pectoris, or their presence in the anamnesis; symptomatic arterial hypertension; chronic cardiac failure above NYHA class II; diabetes mellitus or impaired glucose tolerance; significant or moderate atherosclerotic changes in the vessels of the eyeground.

All patients underwent a complex clinical and instrumental examination according to the generally accepted standards, and in all cases the diagnosis of the I- and II-stage CCI was verified.

The examination methods included a clinical assessment of the neurological status; the severity of cognitive impairment was assessed by the Global Deterioration Rating scale (Folstein et al. 1975), the Montreal Cognitive Scale (MoCA), MRI of the brain (Philips apparatus, with magnetic intensity of 0.3 Tesla). All the examined subjects received consultation from an ophthalmologist and a cardiologist.

Assessment of clinical and laboratory data and a neurological status in the main group was undertaken at the beginning and two weeks after the treatment. Evaluation of cognitive dysfunction was carried out two months after the comprehensive treatment (in the main group). To objectify and unify the assessment of changes in the well-being and neurological status, there was used a rating scale developed by the authors to determine the severity of the disorders (Shulginova et al. 2014, Shulginova et al. 2015).

The treatment was consistent with the principles of evidence-based medicine, all the patients were on a nitrate-free diet.

All the patients in the main groups received a basic pharmacological therapy every day for 14 days: an angiotensin-converting enzyme inhibitor enalapril maleate (Berlipril), (supporting antihypertensive therapy) and a vasoactive drug – ethyl ester of apovincamic acid (Bravinton, Vinpocetine, Vincetin, Cavinton).

The study design and the drugs that the patients of the main groups received are shown in Table 1.

The used pharmacological preparations and the schemes of their administration in patients with CCI are shown in Table 2. All the drugs were administered according to the recommendations described in the reference book "Lekarstvennye sredstva (*Medicines*)" (Mashkovskiy M.D., 2001) and the instructions and annotations attached thereto.

Assessment of clinical and laboratory data in the main groups was performed at the beginning of the treatment and two weeks after the end of the treatment.

Cytokines (TNFα, IL-1β, IL-6, IL-8, IFNγ, IL-2, IL-17, IL-18, G-CSF, IL-4, IL-10, IL-1RA) were detected by solid-phase ELISA using kits made by Vector-Best (Russia), components of the complement system (C_3, C_{3a}, C_4, C_5, C_{5a}) and factor H by the diagnostic kit made by Cytokine Ltd. (Russia). The activity of the C_1-inhibitor was determined by the chromogenic method by its ability to inhibit C_1-esterase. The registration of all ELISA results was carried out using a microplate reader "Sunrise", Tecan (Austria).

The phagocytic activity of polymorphonuclear leukocytes after their isolation from blood on a Ficoll-Urografin gradient (with d = 1,077) was evaluated according to the standard procedure determining phagocytic index (PI), phagocytic number (PN), and the phagocytosis activity index (PAI). The activity of oxygen-dependent neutrophil systems was evaluated using a spectrophotometer PD-303 (Apel, Saitama, Japan) basing on the reduction reaction of nitroblue tetrazolium (NBT-test), spontaneous and stimulated with zymosan (NBT-sp, NBT-st), the neutrophil stimulation index (SI) and the neutrophil functional reserve (FR).

Statistical processing of the study results was carried out according to the criteria of the variance statistical analysis with computing of the mean (M), the the arithmetic mean error (m) with the help of the Microsoft Excel software package, 2010. The significance of difference was assessed by the U-criterion. Differences with $p < 0.05$ were considered statistically significant.

Results and discussion

The original purpose of the study was to detect immune disorders in patients with associated with hypertension depending on the stage of the disease.

Before starting the treatment, an increased concentration of proinflammatory cytokines was detected in blood plasma of the patients: TNFα, IL-1β, IL-6, IL-8, IL-17 and IL-18, an increase being 4.4, 2.4, 5.5, 5.9, 1.2, and 2.6 times, respectively, of anti-inflammatory cytokines: IL-4, IL-10 and IL-1RA with an increase of 8.0, 1.4 and 1.1 times, respectively. The content of IFNγ, IL-2, and G-CSF growth factor turned out to be 1.4, 45.0 and 1.7 times higher than the parameters of the healthy donors, respectively (Table 3).

In case of CCI II stage, the similarly oriented changes in the content of cytokines were revealed in blood plasma. The levels of TNFα, IL-1β, IL-6, IL-8, IL-17 and IL-18 turned out to have increased 5.2, 2.1, 5.8, 9.0, 2.6 and 2.8 times, respectively. The content of IL-4, IL-10 and IL-1RA increased correspondingly 20.0, 1.4 and 1.2 times, and that of IFNγ, IL-2 and G-CSF increased 1.5, 48.6 and 1.9 times (Table 3).

In blood plasma of the patients with I and II stage of CCI before starting the treatment, a decrease in the content of C_3 and C_5-components of the complement, C_1-inhibitor, an increase in C_{3a} and C_{5a} components was detected, while the level of C_4 remained within the normal range. The concentration of the inhibitor-factor H in case

Table 1. Distribution of patients by the method of administered pharmacotherapy

Patients	Group	Pharmacotherapy	Count
Basic pharmacological therapy		**Berlipril, Cavinton**	104
CCI – I stage	1	Cereton and Actovegin	12
	2	Ceraxon and Mexicore	12
	3	Ceracson, Mexicor and Glutoxim	14
	4	Ceracson and Mexicor and Polyoxidonium	14
CCI – II stage	1	Cereton and Actovegin	12
	2	Ceraxon and Mexicore	12
	3	Ceracson, Mexicor and Glutoxim	14
	4	Ceracson and Mexicor and Polyoxidonium	14
		Total	104
		Donors	22

Table 2. Drugs administered and drug dosage regimens for patients with CCI

Drug name	Drug dosage regimens
Basic pharmacotherapy	
BERLIPRIL Latin name: Berlipril International name – Enalarpil Trade names: Enalapril, Bagopril®, Berlipril® Vasoprene, Invoril®, Renipril®, Renitec, Ednit, Enalapril maleate, Enam®, Enap®, Enarenal®, Enafarm, Envas, Enipril Chemical name: (S)-1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline (as maleate) Drug form: tablets Manufacturer: Berlin-Chemie AG/Menarini Group (Germany), Berlipril® plus. Closed Actioner Sosety Berlin-Farma, Russia Identification Number: П №012342/01-2000 25.10.00ППР Pharmacotherapeutic group: ACE inhibitors	10 mg a day orally, in 24 hours № 14
VINPOCETINE Latin name: Vinpocetinum International non-proprietary name (established name): Vinpocetine Brand name: Vinpocetine Chemical name: ethyl-(3alpha, 16alpha)-eburnamene-14-carboxylate Drug form: tablets, infusion solution Manufacturer: Closed Actioner Sosety Sotex Pharm Firma, Russia Identification number: R N003245/01 (2030-06-09– 0000-00-00) Pharmacotherapeutic group: cerebral blood flow improver	10 mg in 200,0 ml 0,9% solution of sodium chloride intravenously, by drop infusion, in 24 hours № 14
Immunomodulators	
POLYOXIDONIUM Latin name: Polyoxidonium International non-proprietary name (established name): Azoximeri bromidum Brand name: Polyoxidonium® Chemical name: copolymer of 1,4-ethylene-piperazine N-oxide and (N-carboxymethyl)-1,4-ethylene-piperazinium bromide Drug form: vaginal and rectal suppositories, tablets, injection solution and drop solution Manufacturer: NPO Petrovax Farm, Russia Identification number: R N002935/04 Pharmacotherapeutic group: immunomodulator	6 mg (intramuscularly), 8 times (daily for the first 2 days, then every second day)
GLUTOXIM Latin name: Glutoxim International non-proprietary name (established name): Glutamyl-Cysteinyl-Glycine Disodium Brand name: Glutoxim® Chemical name: bis-(gamma-L-glutamyl)-L-cysteinyl-bis-glycine disodium salt Drug form: injection solution Manufacturer: Closed Actioner Sosety Farma Vam, Russia Identification number: R N002010/01-290908 Pharmacotherapeutic group: immunostimulator	30 mg in 1 ml of 3% solution, intramuscularly, in 24 hours № 14

Drug name	Drug dosage regimens
Antioxidants/antihypoxants	
MEXICORE Latin name: Mexicor International non-proprietary name (established name): Ethyl methylhydroxypyridine succinate (Ethylmethylhydroxypyridine succinate) Brand name: Mexidol®, Ethylmethylhydroxypyridine succinate, Mexifin®, Mexident®Mexicor®, Mexipur Chemical name: 2-ethyl-6-methyl-3-hydroxypyridine succinate Drug form: capsules, intravenous and intramuscular solutions Manufacturer: OOO EcoPharmInvest, Russia Identification number: R №001245/01 (2010-09-08– 0000-00-00) Pharmacotherapeutic group: antioxidant	200 mg in 24 hours, intramuscularly, stream infusion for 5 min, № 14
ACTOVEGIN Latin name: Actovegin International non-proprietary name (established name): Deproteinized calf blood haemoderivative Brand name: Actovegin® Chemical name: deproteinized calf blood haemoderivative Drug form: tablets, gel, infusion and injectios solutions Manufacturer: Closed Actioner Sosety Sotex Pharm Firma, Russia Identification number: JIC-001323 Pharmacotherapeutic group: antihypoxic drug, tissue regeneration stimulator	200 mg of Actovegin (Nycomed Austria GmbH, Austria) in 5 ml, intramuscularly, stream infusion, in 24 hours № 14
Nootropics	
CERAXON Latin name: Ceraxon International non-proprietary name (established name): Citicoline Brand name: Ceraxon® Drug form: tablets, intramuscular and intravenous solutions, solution for oral administration Manufacturer: Ferrer Internacional SA (Spain) Identification number: JICP-000089-250116 Pharmacotherapeutic group: nootropic	1000 mg intramuscularly, stream infusion, in 24 hours № 14
CERETON Latin name: Cereton International non-proprietary name (established name): Choline Alfoscerate Brand name: Cereton® Drug form: intravenous and intramuscular solutions, capsules Manufacturer: Closed Actioner Sosety Sotex Pharm Firma, Russia Identification number: JICP-005608/09 (2013-07-09– 0000-00-00) Pharmacotherapeutic group: nootropic	1000 mg intramuscularly, stream infusion, in 200,0 ml of 0,9% solution of sodium chloride, in 24 hours № 14

of CCI I stage did not differ from the values of the donors, but decreased in case of CCI II stage(Table 4).

The results of studying the functional metabolic activity of peripheral blood neutrophils were found to be slightly different in the patients with CCI I stage and CCI II stage when admitting to hospital: no changes in the activity and intensity of phagocytosis (PI, PN and PAI) compared to those of the healthy donors, an increase in NBT-sp along with a decrease in SI in the patients with CCI I stage and an increase in case of II stage of the studied parameters of the activity of oxygen-dependent polymorphonuclear leukocyte systems (NBT-sp, NBT-st, FR), except for SI (Table 5).

Thus, out of 26 investigated parameters of immune status in the patients with CCI I stage and CCI II stage at the time of admission to the clinic, 73.1% and 80.8% of the indicators, respectively, were different from the values of the healthy donors, 14 (66.7%) parameters in the patients with both stages of CCI were the same in size and in the direction of the changes, another 5 (19.2%) were identical in the direction. The exceptions were the markers of oxygen-dependent activity of circulating neutrophils: NBT-st and FR were higher in patients with CCI II stage compared with their normal parameters in case of CCI I stage. SI was found to be decreased in case of stage I with its normal value in case of stage II. In addition, the concentration of the inhibitor of the complement system, Factor H, was reduced in case of CCI stage II, with its normal value in case of CCI I stage (Table 3–5).

For a qualitative comparison of the affected indicators, their analysis was carried out according to a level, with dividing the intensity of disorders into degrees (Zemskov et al. 2013). At the same time, it was revealed that the I degree of disorders included 7 (26.9%) indocators, and II and III degrees, respectively, included 4 (15.4%) and 8 (30.8%) indicators, which required mandatory correction (Zemskov et al. 2013, Konoplya et al. 2013, Konoplya et al. 2015). In the group of the patients with CCI I stage and CCI II

Table 3. Cytokine spectrum of blood plasma in case of CCI stage I and II before treatment (M ± m)

Parameters	Units	1 Healthy	2 CCI-I	3 CCI-II
IL-17	pcg/ml	8.7±0.2	10.5±0.3*1	22.6±0.9*1,2
IL-18	pcg /ml	47.6±2.1	124.4±4.2*1	135.1±5.0*1
TNFα	pcg /ml	2.9±0.07	12.9±0.3*1	13.5±0.4*1
IL-8	pcg /ml	1.8±0.06	10.6±0.5*1	16.2±0.7*1,2
IL-6	pcg /ml	2.4±0.09	13.3±0.6*1	14.2±0.5*1
IL-1β	pcg /ml	5.3±0.2	12.0±0.4*1	11.3±0.3*1
IL-1RA	pcg /ml	137.7±1.7	149.3±2.5*1	167.8±1.6*1,2
IL-10	pcg /ml	2.7±0.13	3.7±0.1*1	3.9±0.1*1
IL-4	pcg /ml	0.4±0.04	3.2±0.08*1	8.0±0.3*1,2
IFNγ	pcg /ml	15.6±0.3	22.4±0.5*1	23.6±0.7*1
G-CSF	pcg /ml	12.3±1.0	20.3±0.8*1	23.6±1.1*1,2
IL-2	pcg /ml	0.14±0.02	6.3±0.3*1	6.8±0.4*1

Note: here and in other tables: the asterisk marks significant differences in the arithmetic mean ($p<0.05$); figures next to the asterisk show in relation to indicators of which group these differences are given.

Table 4. State of the complement system in case of CCI I stage and CCI II stage before treatment (M ± m)

Parameters	Units	1 Healthy	2 CCI-I	3 CCI-II
C_3	mg/dL	82.2±1.5	66.3±1.7*1	65.1±2.4*1
C_{3a}	ng/ml	38.2±2.1	47.1±0.8*1	47.3±1.9*1
C_4	mg/dL	24.0±0.5	25.1±0.9	25.8±0.7
C_5	mg/dL	0.1±0.01	0.05±0.006*1	0.05±0.005*1
C_{5a}	ng/ml	78.4±3.5	127.4±3.1*1	127.3±4.2*1
C_1-inh.	ng/ml	288.5±3.0	272.5±2.3*1	274.7±2.4*1
Factor H	ng/ml	39.7±1.0	39.5±1.5	36.8±0.7*1,2

Table 5. Functional and metabolic activity of circulating blood neutrophils in CCI I stage and CCI II stage before treatment (M ± m)

Parameters	Units	1 Healthy	2 CCI-I	3 CCI-II
PI	%	82.8±2.3	79.1±1.7	78.9±2.8
PN	abs.	7.9±0.4	7.2±0.3	7.8±0.4
PAI	–	6.6±0.4	5.7±0.5	6.4±0.3
NBT-sp	%	7.5±0.4	9.9±0.1*1	11.0±1.2*1
NBT-st	%	25.1±2.4	26.7±1.1	37.5±2.9*1,2
FR	%	17.6±2.3	16.8±1.1	26.5±2.1*1,2
SI	–	3.8±0.6	2.7±0.1*1	3.4±0.3*2

stage, 21 (80.8%) parameters were found tobe disrupted, of which 5 (19.2%) with the I degree, and 5 (19.2%) and 11 (42, 3%) with II and III degrees, respectively (Table 6).

The results obtained show that in patients with CCI I and II stages associated with AH, there are similar changes in the parameters of the immune status, which indicates the presence of immune inflammation, but at the same time it was established that in case of stage II of the disease 9 (34.6%) indicators are more evident or radically different. The latter concerns the increased indices of oxygen-dependent activity of circulating neutrophils in case of CCI II stage, which can be considered as the most important link in the further development of inflammation (Karaulov and Kalyuzhin).

When comparing the changes in the neuropsychic status in patients with CCI I and II stages, the results obtained are shown in Table 7.

The patients with CCI I and II stages before being treated had stereotypical complaints. They were disturbed by intensive periodic and/or permanent cephalgia localized in the frontal and temporal regions; pronounced and mild dizziness, unsteadiness when walking, whistling and buzzing in the ears, weakness in the limbs; sleep disturbance, decreased memory and attention, emotional lability, tearfulness and irritability.

In case of CCI I statge, pre-treatment period was dominated by subjective disorders in the form of headaches, dizziness, emotional lability, sleep disturbance, and me-

Table 6. Changes in immune parameters in case of CCI I stage and II stage before treatment

Experimental conditions	Changed indicators		Changed indicators according to degree of disorder					
			I		II		III	
	Abs.	%	Abs	%	Abs	%	Abs	%
CCI I stage	19	73.1	7	26.9	4	15.4	8	30.8
CCI II stage	21	80.8	5	19.2	5	19.2	11	42.3

Table 7. Neuropsychiatric status before treatment in case of CCI I and II stages (M±m)

Parameters	1 Healthy	2 CCI-I	3 CCI-II
Subjective disorders	0.4±0.02	2.52±0.05^{*1}	2.85±0.06^{*1,2}
Neurological symptoms	0	1.45±0.04^{*1}	2.3±0.04^{*1,2}
Cognitive deterioration on GDR scale	0.15±0.01	1.85±0.06^{*1}	2.75±0.05^{*1,2}
Cognitive deterioration on Monreal scale	27.1±0.3	21.3±0.4^{*1}	18.8±0.7^{*1,2}

mory loss. In case of CCI II statge, the dominating complaints were non-systemic vertigo, cephalgic syndrome of clearer localization, the asthenic complex symptoms were less prominent, while the total score was statistically higher than that at I stage of the disease (Table 7).

When assessing the neurological status of the patients prior to treatment, cerebral organic symptoms were identified that were then integrated into the following syndromes: vestibulopathic, pyramidal, cerebellar, of cognitive dysfunction, psychopathological, and pseudobulbar. The mean values of the total score of the neurological status with CCI I stage were 1.45±0.04, with II stage 2.3±0.04, which indicates an increase in the distinctive focal symptomatology. The overall assessment of cognitive impairment in patients with with CCI I stage according to the Montreal scale before treatment was 21.3±0.4, and according to the Cognitive deterioration on Monreal scale – 1.85±0.06 points. In case of state II of the disease, a higher degree of cognitive impairment was identified, as indicated by the corresponding scores: 18.8±0.7 and 2.75±0.05, which suggests possible mild dementia (Table 7).

Thus, incase of II stage of the disease, all the parameters of the neuropsychic status were more pronounced, but the majority of the studied immune parameters turned out to be identical in quantity and quality in case of both stages of the disease, which can mean that there is immune inflammation already in case of CCI I stage, which requires the use of specilized immunocorrection.

In the previous description of the results, it was proved necessary to use in case of CCI immunomodulators in a complex pharmacotherapy, which includes antioxidant, nootropic and metabolic drugs. In this connection, we studied the effectiveness of immunomodulators – glutoxim and polyoxidonium when correcting immune and clinical disorders in chronic ischemia of the brain of the first stage.

In case of CCI I stage, prior to the treatment, it was determined that on the systemic level (circulating blood plasma) there was an increase in the concentration of pro- (TNFα, IL-1β, IL-6, IL-8, IL-17 and IL-18) and anti-inflammatory cytokines (IL -4, IL-10 and IL-1RA). The content of IFNγ, IL-2 and growth factor G-CSF was also found to be higher than the parameters of the healthy donors. After use in the treatment of ceraxon and mexicor, the concentration of IL-1β and IL-1RA normalized, IL-10 increased even more, the level of IFNγ, IL-2, G-CSF and IL-4 did not change, and the content of the other cytokines studied shifted towards the parameters of the healthy donors. In the patients treated, along with ceraxon and mexicore, with glutoxim, the concentration of IL-17 got normalized, compared with the previous group of patients; the content of TNFα, IL-6, IL-8, IL-18 and IL-2 got modified to an even greater extent, but not to reach the parameters of the norm. At the same time the level of anti-inflammatory cytokines (IL-4, IL-10 and IL-1RA), IL-1β, IFNγ, G-CSF remained unchanged. The use of polyoxidonium, in comparison with the use of ceraxon and mexicor, resulted in the normalized concentration of TNFα and IL-17, corrected, but not up to the parameters, IL-6, IL-8, IL-18, IL-2 and G-CSF and even to a greater extent increased the content of IL-4 and IL-1RA. The content of IL-10 and IFNγ remained unchanged (Table 8).

It should be noted that polyoxidonium is more effective than glutoxim, because, when compared, TNFα concentration got normalized, IL-6, IL-8, IL-2 and G-CSF levels were more corrected to a greater extent, and the content of IL-4 and IL-1RA increased.

In patients with CCI I stage before starting the treatment, in blood plasma there was determined a decrease in the content of C_3 and C_5-components of the complement, C_1-inhibitor, and an increase in the concentration of C_{3a} and C_{5a}-components, while the level of C_4 and factor H inhibitor remained within the normal range.

After the treatment, including ceraxon and mexicor, the concentration of C_3 and C_{3a} complement components was normalized in patients and the level of C_5 and C_{5a} was corrected towards the value of healthy donors. The use of glutamim additionally normalized the content of C_5 complement component and the C_1-inhibitor. In comparison with glutoxim, polyoxidonium additionally normalized the concentration of C_{5a} component of the complement (Table 9).

Table 8. Cytokine spectrum of blood plasma in case of CCI I stage when using glutoxime and polyoxidonium (M±m)

Parameters	Unit	1	2	3	4	5
			CCI-1			
				After treatment		
		Healthy	Before treatment	Ceraxon + Mexicore	Ceraxon + Mexicor + Glutoxime	Ceraxon + Mexicor + Polyoxidonium
IL-1RA	pkg/ml	137.7±1.7	149.3±2.5*1	133.9±2.6*2	139.2±2 .7*2	149.2±3.0*1-4
IL-10	pkg/ml	2.7±0.13	3.7±0.1*1	8.4±0.3*1,2	8.9±0.3*1,2	8.6±0.3*1,2
IL-4	pkg/ml	0.4±0.04	3.2±0.08*1	3.2±0.2*1	3.8±0.2*1	4.7±0.5*1-3
IL-8	pkg/ml	1.8±0.06	10.6±0.5*1	6.2±0.3*1,2	3.9±0.1*1-3	2.0±0.06*2-4
IL-17	pkg/ml	8.7±0.2	10.5±0.3*1	9.5±0.2*1,2	8.8±0.2*2,3	9.0±0.3*2,3
IL-18	pkg/ml	47.6±2.1	124.4±4.2*1	94.2±4.5*1,2	55.5±1.9*1-3	60.3±5.7*1-3
TNFα	pkg/ml	2.9±0.07	12.9±0.3*1	8.1±0.4*1,2	4.1±0.3*1-3	3.0±0.1*2-4
IL-1β	pkg/ml	5.3±0.2	12.0±0.4*1	5.4±0.1*2	5.7±0.3*2	5.2±0.2*2
IL-6	pkg/ml	2.4±0.09	13.3±0.6*1	8.6±0.9*1,2	4.3±0.5*1-3	2.9±0.1*2-4
G-CSF	pkg/ml	12.3±1.0	20.3±0.8*1	18.3±1.4*1	16.8±1.0*1	14.0±1.3*1-4
IL-2	pkg/ml	0.14±0.02	6.3±0.3*1	5.9±0.8 *1	3.2±0.4*1-3	2.4±0.2*1-4
IFNγ	pkg/ml	15.6±0.3	22.4±0.5*1	22.2±0.9*1	18.3±1.1*1	22.7±1.3*1

Table 9. The complement system for CCI of the first stage against the background of the use of glutoxime and polyoxidonium (M±m)

Parameters	Unit	1	2	3	4	5
			CCI-1			
				After treatment		
		Healthy	Before treatment	Ceraxon + Mexicore	Ceraxon + Mexicor + Glutoxime	Ceraxon + Mexicor + Polyoxidonium
C_3	mg/dl	82.2±1.5	66.3±1.7*1	83.8±3.9*2	82.4±1.3*2	84.2±4.3*2
C_4	ng/ml	24.0±0.5	25.1±0.9	23.8±1.4	28.6±1.0	25.5±1.7*4
C_5	mg/dl	0.1±0.01	0.05±0.006*1	0.07±0.005*1,2	0.09±0.02*2	0.11±0.01*2,3
C_{3a}	mg/dl	38.2±2.1	47.1±0.8*1	40.3±2.6*2	36.1±0.9*2,3	44.4±3.2*2,4
C_{5a}	ng/ml	78.4±3.5	127.4±3.1*1	91.3±4.9*1,2	101.3±3.8*1,2	77.7±3.2*2-4
Factor H	ng/ml	39.7±1.0	39.5±1.5	40.5±1.1	39.5±0.5	41.9±0.7
C_1-inh.	ng/ml	288.5±3.0	272.5±2.3*1	278.8±2.2*1	291.2±2.8*2,3	302.2±4.4*1-4

In case of CCI I stage, there was found no change in either activity and intensity of phagocytosis (PI, PN and PAI) compared with those of the healthy donors, and an increase in NBT-sp with a decrease in SI. The use of ceraxon and mexicor did not change the value of finctional metabolic activity of polymorphonuclear leukocytes of peripheral blood. The use of glutoxime, in comparison with its absence in treatment, corrects NBT-sp, but not to the values of healthy donors, and the use of polyoxidonium additionally normalizes SI (Table 10).

During the comparative analysis of the neuropsychic status in the patients with CCI-I when using different treatment regimens, the results presented in Table 11 were obtained.

When the combination of ceraxon and mexicore was used in therapy, the total score intensity of subjective disorders was 1.72 0.09; the total intensity score of neurologic sym ptoms was 1.09±0.08, and the total score on the Global Disability Rate scale and on the Montreal scale in the group of patients with CCI-I was 1.41±0.13 and 24.58±0.6; which indicates a positive trend when using these drugs. Co-administration of glutoxime with ceraxon and mexidol brought the scores characterizing subjective disorders closer to the values of the healthy donors (0.94±0.03) and normalized the indicators of cognitive impairment according to the Montreal scale (26.34±0.46), without influence on the indicators of neurological symptoms and cognitive impairment on the GDR scale.

More positive clinical dynamics is observed when using together ceraxon, mexicor and polyoxidonium, as in patients with CCI-I, when using this treatment regimen, the score of subjective disorders was normalized to 0.5±0.08, cognitive indicator on the Montreal scale to 26.51±0.57, the scores of neurologic symptoms were corrected towards the indicators of the healthy donors, but not to their level, to 0.62±0.02 and cognitive impairment on the GDR scale to 1, 09±0.05 (Table 11).The obtained results indicate that in patients with CCI associated with hypertensive disease, significant immune and clinical disorders were detected, and the treatment with various combinations of nootropic, antioxidant and immunomodulating medications did not normalize some of

Table 10. Functional-metabolic activity of blood neutrophils in CCI-I when using glutoxime and polyoxidonium (M±m)

Parameters	Unit	1	2	3	4	5
			CCI-1			
				After treatment		
		Healthy	Before treatment	Ceraxon + Mexicore	Ceraxon + Mexicor + Glutoxime	Ceraxon + Mexicor + Polyoxidonium
PI	%	7.5±0.4	9.9±0.1*1	9.9±0.3*1	9.0±0.2*1-3	8.6±0.5*1-3
PN	abs.	25.1±2.4	26.7±1.1	23.2±2.7	22.0±2.4	26.1±3.1
PAI	-	3.8±0.6	2.7±0.1*1	2.4±0.3*1	2.5±0.2*1	3.2±0.3*2-4
NBT-sp	%	17.6±2.3	16.8±1.1	13.3±2.7	13.2±1.4	17.5±3.2
NBT-st	%	82.8±2.3	79.1±1.7	79.5±4.1	83.0±3.5	85.2±5.7
FR	%	7.9±0.4	7.2±0.3	7.8±0.8	6.9±0.9	7.6±0.9
SI	-	6.6±0.4	5.7±0.5	6.3±0.9	5.7±0.8	6.4±0.9

Table 11. Neuropsychic status in CCI-I when using glutoxim and polyoxidonium (M±m)

Parameters	1	2	3	4	5
		CCI-1			
			After treatment		
	Healthy	Before treatment	Ceraxon + Mexicore	Ceraxon + Mexicor + Glutoxime	Ceraxon + Mexicor + Polyoxidonium
Subjective disorders	0.4±0.02	2.52±0.05*1	1.72±0.09*1,2	0.94±0.03*1-3	0.5±0.08*2,3
Neurological symptom	0	1.45±0.04*1	1.09±0.08*1,2	1.04±0.04*1,2	0.62±0.02*1-4
Cognitive deterioration on GDR scale	0.15±0.01	1.85±0.06*1	1.41±0.13*1,2	1.33±0.03*1,2	1.09±0.05*1-4
Cognitive deterioration on Monreal scale	27.1±0.3	21.3±0.4*1	24.58±0.6*1,2	26.34±0.46*2,3	26.51±0.57*2,3

the altered parameters under study, in these conditions pharmacotherapy with using polyoxidonium has the best corrective effect.

Further, the effectiveness of incorporating glutoxime and polyoxidation into complex pharmacotherapy in case of CCI-II was studied.

In patients with CCI-II prior to treatment, in blood plasma there was found an increase in the the level of all the cytokines tested: pro-inflammatory (TNFα, IL-1β, IL-6, IL-8, IL-17 and IL-18), anti-inflammatory (IL-4 , IL-10 and IL-1RA), IFNγ, IL-2 and G-CSF. The treatment, including ceraxon and mexicor, normalized the concentration of IL-1β, reduced but not the values of the healthy donors, the content of other pro-inflammatory cytokines and G-CSF, even more increased the concentration of IFNγ and anti-inflammatory cytokines (IL-4 and IL-1RA), without affecting the high levels of IL-10 and IL-2. The incorporation of glutoxime into complex pharmacotherapy, in comparison with the previous group of patients, normalized the content of IL-17 and G-CSF, shifted aside, but not to the values of the healthy donors, the concentration of TNFα, IL-6, IL-8, IL-18, even more increased the level of IL-10, without affecting the concentration of the remaining cytokines under study. In the patients treated with polyoxidonium, in comparion with glutoxim, the content of anti-inflammatory cytokines IL-10 and IL-1RA even more increased and the concentration of IL-6, IL-8, IL-18 and IL-2 moved towards the norm (Table 12).

In the blood plasma of the patients with CCI-II before the treatment, there was found a decrease in the content of C_3 and C_5-components and inhibitors of the complement system (C_1-inhibitor and factor H), an increased level of C_{3a} and C_{5a} components, whereas the C_4 level remained within the normal range. After including ceraxon and mexicor into pharmacotherapy, the concentration of the C_{3a}-component of the complement and the factor H inhibitor was normalized, the levels of C_3, C_5 and C_{5a} complement components shifted towards the values of the healthy donors. Inclusion of immunomodulating glutoxim additionally into the pharmacotherapy scheme, in comparison with ceraxon and mexicor, normalized the content of the C_3 and C_5 components of the complement and the C_1-inhibitor in the blood plasma of the patients. The use of polyoxidonium, in comparison with glutoxim, additionally increased the concentration of inhibitors of the complement system (C_1 inhibitor and factor H) (Table 13).

Studying functional metabolic activity of peripheral blood neutrophils showed no changes in activity and intensity of phagocytosis (PI, PN and PAI) compared with the healthy donors and an increase in the studied parameters of the activity of oxygen-dependent polymorphonuclear leukocyte systems (NBT-sp, NBT-st, FR) except for SI. After using ceraxon and mexicor in the treatment, the indices of the functional-metabolic activity of neutrophils did not change. Including immunomodulators glutoxim or polyoxidonium in the pharmacotherapy scheme nor-

Table 12. Cytokine spectrum of blood plasma in patients with CCI II stage before treatment with glutoximomie and polyoxidonium (M±m)

Parameters	Unit	1	2	3	4	5
			CCI-II			
				After treatment		
		Healthy	Before treatment	Ceraxon + Mexicore	Ceraxon + Mexicor + Glutoxime	Ceraxon + Mexicor + Polyoxidonium
IL-4	pkg/ml	0.4±0.04	8.0±0.3*1	13.8±1.4*1,2	14.8±1.7*1,2	14.1±1.3*1,2
IL-10	pkg/ml	2.7±0.13	3.9±0.1*1	4.1±0.1*1	6.8±0.3*1-3	8.3±0.6*1-4
IL-1RA	pkg/ml	137.7±1.7	167.8±1.6*1	178.0±3.3*1,2	177.2±3.1*1,2	196.7±3.8*1-4
TNFα	pkg/ml	2.9±0.07	13.5±0.4*1	7.8±0.3*1,2	5.9±0.3*1-3	5.5±0.2*1-3
IL-17	pkg/ml	8.7±0.2	22.6±0.9*1	15.3±0.7*1,2	8.9±0.4*2,3	8.3±0.5*2,3
IL-18	pkg/ml	47.6±2.1	135.1±5.0*1	96.8±5.2*1,2	67.4±4.3*1-3	52.8±2.7*1-4
IL-1β	pkg/ml	5.3±0.2	11.3±0.3*1	5.2±0.7*2	5.7±0.2*2	5.4±0.2*2
IL-6	pkg/ml	2.4±0.09	14.2±0.5*1	10.5±0.7*1,2	7.4±0.9*1-3	3.9±0.07*1-4
IL-8	pkg/ml	1.8±0.06	16.2±0.7*1	11.0±0.8*1,2	8.3±0.9*1-3	2.5±0.05*1-4
IFNγ	pkg/ml	15.6±0.3	23.6±0.7*1	28.6±0.8*1,2	27.4±1.3*1,2	35.8±1.9*1,2
IL-2	pkg/ml	0.14±0.02	6.8±0.4*1	7.8±1.3*1	7.4±0.8*1	2.7±0.8*1-4
G-CSF	pkg/ml	12.3±1.0	23.6±1.1*1	20.2±2.2*1,2	15.2±2.1*2,3	14.3±1.0*2,3

Table 13. Complement system in patients with CCI II stage before treatment with glutoxim and polyoxidonium (M±m)

Parameters	Unit	1	2	3	4	5
			CCI-II			
				After treatment		
		Healthy	Before treatment	Ceraxon + Mexicore	Ceraxon + Mexicor + Glutoxime	Ceraxon + Mexicor + Polyoxidonium
C_3	mg/dl	82.2±1.5	65.1±2.4*1	72.4±1.8*1,2	78.9±2.6*2,3	81.2±2.4*2,3
C_4	ng/ml	24.0±0.5	25.8±0.7	24.8±1.2	26.8±1.6	25.3±1.3
C_5	mg/dl	0.1±0.01	0.05±0.005*1	0.07±0.004*1,2	0.1±0.01*2,3	0.09±0.01*2,3
C_{3a}	mg/dl	38.2±2.1	47.3±1.9*1	39.9±2.7*2	42.4±2.8*2	42.5±2.5*2
C_{5a}	ng/ml	78.4±3.5	127.3±4.2*1	105.6±7.8*1,2	99.5±5.8*1,2	101.3±4.3*1,2
Factort H	ng/ml	39.7±1.0	36.8±0.7*1	40.7±2.6*2	41.9±1.0*2	55.6±2.4*1-4
C_1-inh.	ng/ml	288.5±3.0	274.7±2.4*1	273.3±2.6*1	291.2±2.6*2,3	306.4±3.2*1-4

malizes NBT-sp and reduces, but not to the level of the healthy donors' indicators, NBT-st and FR, without affecting SI (Table 14).

The use of ceraxon and mexicor in the pharmacotherapy of patients with CCI-II corrected, but significantly not to the level of the healthy donors, all the indicators of neuropsychiatric status: the total score of intensity of subjective disorders and neurologic symptomsto to 1.7±0.1 and 1.65±0.12, respectively; the total score on the GDR scale and the Montreal scale to 1.9±0.1 and 24.0±0.71. The addition of glutoxim to ceraxon and mexicor, brought even closer to the values of the healthy donors the scores characterizing subjective disorders (1.21±0.09), neurologic symptoms (1.4±0.04) and cognitive impairment on the GDR scale (1.61±0,13), without affecting the indicators of cognitive impairment according to the Montreal scale (24.31±0.71). More positive clinical dynamics is observed when using together ceraxon, mexicor and polyoxidonium, as in patients with CCI-II, when this treatment regimen was applied, there was a more evident correction towards the indicators of the healthy donors of the total score of subjective disorders, neurological symptoms and cognitive impairments on the GDR scale to 0.86±0.09, 1.18±0.08 and 1.38±0.49, respectively (Table 15).

Futher, the comparative effectiveness of the applied schemes of pharmacological correction of immune and clinical disorders in CCI stage I and II associated with AH was carried out.

In a quantitative comparison of the number of disturbed immunological parameters under study, it was found that, in case of CCI-I before the treatment, the values of 19 (73.3%) of the parameters under study were different from the norm; besides, it was found out that 26.9% of exchanging parameters had the first degree of disorders, and stage II and III, respectively 15.4% and 30.8% of them. After using ceraxon and mexicore, 57.7% of the indices remained disturbed (19.2%, 11.5% and 26.9% had I, II and III degrees of disorders, respectively). After using ce-

Table 14. Functional-metabolic activity of blood neutrophils in patients with CCI stage II before treatment with glutoximomie polyoxidonium (M ± m)

Parameters	Unit	1	2	3	4	5
			CCI-II			
				After treatment		
		Healthy	Before treatment	Ceraxon + Mexicore	Ceraxon + Mexicor + Glutoxime	Ceraxon + Mexicor + Polyoxidonium
FI	%	82.8±2.3	78.9±2.8	84.1±6.2	80.6±5.1	89.7±9.0
FN	abs.	7.9±0.4	7.8±0.4	7.9±1.1	7.8±0.7	8.9±1.2
IAF	-	6.6±0.4	6.4±0.3	6.8±1.2	6.3±0.6	6.8±0.8
NBT-sp.	%	7.5±0.4	11.0±1.2*1	12.1±1.3*1	8.4±0.9*2,3	8.1±0.6*2,3
NBT-st	%	25.1±2.4	37.5±2.9*1	39.6±4.0*1	29.5±1.2*1-3	29.6±2.2*1-3
FRN	%	17.6±2.3	26.5±2.1*1	27.4±4.1*1	21.1±1.7*1-3	21.5±2.3*1-3
ISN	-	3.8±0.6	3.4±0.3	3.9±0.8	3.5±0.6	3.7±0.3

Table 15. Comparative analysis of indicators of neuropsychiatric status when treating patients with CCI-II with various schemes of pharmacological therapy (M±m)

Parameters	1	2	3	4	5
		CCI-II			
			After treatment		
	Healthy	Before treatment	Ceraxon + Mexicore	Ceraxon + Mexicor + Glutoxime	Ceraxon + Mexicor + Polyoxidonium
Subjective disorders	0.4±0.02	2.85±0.06*1	1.7±0.1*1,2	1.21±0.09*1-3	0.86±0.09*1-4
Neurological symptom	0	2.3±0.04*1	1.65±0.12*1,2	1.4±0.04*1-3	1.18±0.08*1-4
Cognitive deterioration on GDR scale	0.15±0.01	2.75±0.05*1	1.9±0.1*1,2	1.61±0.13*1-3	1.38±0.06*1-4
Cognitive deterioration on Monreal scale	27.1±0.3	18.8±0.7*1	24.0±0.71*1,2	24.31±0.71*1,2	24.35±0.49*1,2

raxon, mexicor and glutoxim, 38.5% remained different from the values of the healthy donors (7.7%, 11.5% and 19.2% had I, II and III degrees of disorders, respectively). The most effective scheme of pharmacotherapy was found to be a combination of ceraxon, mexicor and polyoxidonium, since 26.9% of the indicator happened to be changed, and 7.7%, 7.7% and 11.5% had I, II and III degrees of disorders, respectively (Table 16).

Basic pharmacotherapy in this case is considered to be the least effective combination of ceretone+actovegin, applied simultaneously with the described treatment regimens. At the same time, the combination of ceraxon and mexicor did not differ from ceritone and actovegin in terms of laboratory efficacy in case of CCI-I, and the ceraxon+mexicor+-polyoxidonium scheme (61 points) was more preferable than ceraxon+mexicor+glutoxim (28 points) (Table 17).

In a quantitative comparison of the number of disturbed immunological parameters under study, it was found out that in case of CCI-II before the treatment, 80.8% of the indicators under study were different from the values of the norm; and with that, it was discovered that I and II degrees of disorders had 19.2% and III degree – 42.3% of the indicators. After using ceraxon and mexicore, 73.1% of the indicators (for I and II degrees – 19.2% each and for III – 34.6%) remained disturbed. After using ceraxon, mexicor and glutoxim, 50.0% remained different from the indicators of the healthy donors (for I, II and III degrees – 19.2%, 3.8% and 26.9%, respectively). After combining ceraxon, mexicor and polyoxidonium, 57.7% of the parameters were changed, with that I, II and III degree of disorders had 19.2% of parameters each (Table 18).

Table 16. Comparative immunological efficacy of different schemes of pharmacological therapy for CCI-I

Experimental conditions	Indicators different from those of healthy donors		Changed indicators according to degree of disorder					
			I		II		III	
	total	%	total	%	total	%	total	%
Before treatment	19	73.1	7	26.9	4	15.4	8	30.8
Ceraxon + Mexicore	15	57.7	5	19.2	3	11.5	7	26.9
Ceraxon + Mexicor + Glutoxime	10	38.5	2	7.7	3	11.5	5	19.2
Ceraxon + Mexicor + Polyoxidonium	7	26.9	2	7.7	2	7.7	3	11.5

Table 17. Own corrective effects of various combinations of ceraxon, mexicor, glutoxime and polyoxidonium in case of CCI-I and CCI -I

Pharmacological treatment regimens	Total score of correction indicators
CCI-I	
Ceraxon +Mexicore	0
Ceraxon +Mexicor +Glutoxime	28
Ceraxon +Mexicor +Polyoxidonium	61
CCI-II	
Ceraxon +Mexicore	8
Ceraxon +Mexicor +Glutoxime	42
Ceraxon +Mexicor +Polyoxidonium	34

Table 18. Comparative immunological efficacy of various regimens of pharmacological therapy for CCI-II

Experimental conditions	Indicators different from those of healthy donors		Changed indicators according to degree of disorder					
			I		II		III	
	total	%	total	%	total	%	total	%
Before treatment	21	80.8	5	19.2	5	19.2	11	42.3
Ceraxon + Mexicore	19	73.1	5	19.2	5	19.2	9	34.6
Ceraxon + Mexicor + Glutoxime	13	50.0	5	19.2	1	3.8	7	26.9
Ceraxon + Mexicor + Polyoxidonium	15	57.7	5	19.2	5	19.2	5	19.2

In terms of laboratory efficacy in case of CCI-II, the combination of ceraxon and mexicor was slightly more effective than that of ceriton and actovegin, and the ceraxon+mexicor+glutoxim scheme (42 points) was actually at the same level as the ceraxon+Mexicor+polyoxidonium scheme (34 points) (Table 18).

Discussion

Given that one of the main causes of the immune inflammatory reaction, which is of a metabolic nature, is hypoxia, an increase, that was detected, of the content of pro-inflammatory cytokines and chemokines (TNFα, IL IL-6, IL-6, IL-8, IL-17, IL-18) with a compensatory increase in the concentration of anti-inflammatory cytokines (IL-10, IL-1RA, IL-4) in the systemic circulation of patients with CCI-I and CCI-II reflects the reaction of resident and recruited cells of innate immunity and epithelium to molecular patterns associated with a damage (Zurochka et al. 2013, Yarilin 2010, Loktionov et al. 2015, Pigarevskyy et al. 2014, Lukens et al. 2012, Spenceret al. 2014).

TNFα, the primary mediator of inflammation involved in the pathogenesis of most infectious and immunopathological diseases, coordinates an inflammatory response and the cytokine cascade (IL-1β, IL-6, IL-8). IL-1,the main mediator of the development of the local inflammatory reaction, it is one of the key factors in developing an immune response, including in case of in sterile inflammation, participates in the transformation of local inflammation into a systemic inflammation, stimulates the synthesis of IL-6, TNFα, IL -12, IL-8, IL-23, IFNγ, activates lymphocytes, expression of adhesion molecules on endotheliocytes, increases NO synthase activity, participates in the production of acute inflammation proteins, and demonstrates neuroregulatory activity. Massive production of IL-1β develops with ischemia, and blockade of signaling cascades associated with IL-1 can significantly reduce tissue damage and production of other cytokines. IL-6, a broad-spectrum pro-inflammatory cytokine, participates in the induction of almost the entire complex of local manifestations of inflammation, influences the migration of phagocytes by increasing the production of CC-chemokines that attract monocytes and macrophages and weakening the production of CXC-chemokines that attract neutrophils, induces the production of acute phase proteins by hepatocytes, and increases the activity of cytotoxic T-lymphocytes. The pro-inflammatory chemokine IL-8 provides extravasation of neutrophils and their directed migration to the inflammatory focus, where its sources are macrophages of the inflammatory focus and endothelial cells of the vessels in the inflammatory zone. The IL-8 produced by them provides for attracting neutrophils to the vascular wall, activating their integrins and emigration of a cell from the vessel. In addition, the chemokine stimulates the production of cytokines by mononuclears and exercises an angiogenic effect (
Yarilin 2010, Lukens et al. 2012, Chen et al. 2010).

IL-17 has a pro-atherogenic pro-inflammatory effect through activating the release of IL-1, IL-6, IL-8, TNFα, IFNγ, G-CSF by immunocytes and endothelial cells; induces the formation of VEGF, angiogenic factors; regulates the number of neutrophils; enhances adhesion and penetration of monocytes and neutrophils into the arterial wall, but at the same time there is evidence of the stimulating effect of IL-17 on the production of anti-inflammatory cytokines. IL-18 activates monocytes and macrophages, initiates apoptosis processes, induces the production of IL-8 and IFNγ in T-lymphocytes, macrophages and NK cells, promotes the differentiation of T-lymphocytes

into the Th1 cell line, which underlies the development of pro-inflammatory and pro-atherogenic Th1 immune response, and destabilizes the atherosclerotic plaque (Chen et al. 2010, Simbirtsev 2004, Khaden et al. 2009).

One should also note a high-level of IFNγ (effector of cellular immune response of inflammatory type) and prolonged retention of an increased ratio IFNγ/IL-4 in blood, which does not decrease after treating the patients with either CCI-I or CCI-II. This is indicative of activation of IFNγ-producing NK-cells, being lymphoid cells of the innate immune type I (ILC-1), which provide the polarization of T-cell differentiation towards the T-helper type 1 (Th1), activating macrophages, expressing enzymes responsible for forming active forms of oxygen, NO-synthase, and the formation of NO. Later, ILC-1 and Th1 synergistically support mainly the T-cell response (Chen et al. 2007).

In addition, a significant increase in the concentration of colony-stimutating factor G-CSF and IL-2 was found, which also did not decrease after treating the patients with either CCI-I or CCI-II. G-CSF activates mature neutrophils and supports the growth of both mixed granulocyte-monocyte colonies and individual colonies of granulocytes and monocytes/macrophages. IL-2 has a pronounced ability to induce the activity of virtually all clones of cytotoxic cells, increases the cytolytic function of T-killers and NK-cells, activates monocytes and macrophages, thereby increasing the synthesis and secretion of pro-inflammatory cytokines, chemokines, colony-stimulating factors GM-CSF and causes the accelerated proliferation of T- and B-lymphocytes and the restoration of the functional reserve of macrophages (Ketlinsky and Simbirtsev 2008, Yarilin 2010, Simbirtsev 2004).

An increase, in both CCI stages, of anti-inflammatory cytokines (IL-10, IL-1RA, IL-4) is compensatory in nature, limiting the inflammatory response, whereas at the same time a high level of IL-6 and IL-17 can also have an anti-inflammatory effect along with a significant increase in pro-inflammatory cytokines due to stimulating the production of IL-10, IL-1RA, and cortisol. With that, a significant increase in the level of IL-4 and IL-1Ra should be noted before and after treating the patients with CCI-II, especially when using polyoxidonium in the complex pharmacotherapy (Turmova et al. 2014, Karaulov 2008).

It was determined that in patients with CCI-I and CCI-II, the complement system was activated, with no compensatory increase in factor H inhibitor with a decrease in C1-inh, as evidenced by a decrease in the initial components of the complement C_3 and C_5 with an increase in the levels of fragments C_{3a} and C_{5a} released through activation, being active chemotactic and vasodilating factors, which have anaphylactogenic activity and participate in the reactions of inflammation and hypersensitivity. Moreover, the complement system interacts with other humoral systems activated by inflammatory processes and promotes the involvement of these systems into the immune inflammatory response. Finally, the deposition of the complement components in the immune complexes on biological membranes initiates the development of immunopathology due to attracting macrophages and other effectors of immune inflammation to the lesion focus (Yarilin 2010, Loktionov et al. 2015, Boyadzhyan et al. 2010, Khaitov et al. 2010, Pyokhova et al. 2012, Serebryanaya et al. 2015).

When studying the functional metabolic activity of peripheral blood neutrophils in patients with CCI-I and CCI-II when they are admitted to hospital, there was found no change in the indicators of phagocytosis activity and intensity (FI, FN, and IAF), an increase in NBT-sp. with a decrease in ISN in patients with CCI-I and in case of CCI-II an increase of the majority of the studied parameters of the activity of oxygen-dependent polymorphonuclear leukocyte systems (NBT-sp., NBT-st., FRN). A distinctive feature of the differences in the CCI stages was that in case of CCI-II there was found an increasing the level of oxygen-dependent metabolism of polymorphonuclear leukocytes of peripheral blood that was not compensated for by the pharmacotherapy applied, which indicated an increased production of reactive oxygen intermediates resulting from a respiratory explosion, which can be possibly considered as the most important link in the further development of inflammation at this stage of CCI. The latter refers to the increased value of the indicators of oxygen-dependent activity of circulating neutrophils in case of CCI-II, which can be considered as the most important link in the further development of inflammation (Karaulov and Kalyuzhin 2013, Karaulov et al. 2015, Solovyova et al. 2016).

The principle of treating CCI is to eliminate external factors that affect the increase in blood pressure, constant antihypertensive therapy and the use of drugs optimizing cerebral blood flow, neurotransmitter and metabolic activities, with pronounced antioxidant and antihypoxic effects, having a multifactorial effect on the brain tissue and creating neurometabolic protection of brain cells from ischemia and hypoxia, enhancing reparative processes in the brain (Levin et al. 2014, Putilina 2016, Suslina et al. 2011, Putilina 2014, Chukanova and Chukanov 2014, Schmidtke and Hull 2005).

Taking into account the results of our evaluation of the immunometabolic status in this category of patients, it is necessary to use various combinations of nootropic, antioxidant and immunomodulating drugs in a comprehensive pharmacological therapy.

The mechanism of the energy-correcting action of mexicor (2-ethyl-6-methyl-3-hydroxypyridine succinate – EMHPS) is connected with a specific influence of succinate on energy metabolism, which, in case of hypoxia, when entering the intracellular space, can get oxidized in Krebs cycle. In case of hypoxia, succinate supports activity of FAD-dependent link of the Krebs cycle, catalyzed by succinate dehydrogenase, and provides enhanced compensatory activation of aerobic glycolysis and reduced inhibition of oxidative processes in the TCA cycle which increases the content of ATA and creatine phosphate in anaerobic conditions, activates the energy-synthesizing functions of mitochondria, which, under hypoxic conditions, allows maintaining energy production in the cell

for a certain time period. At the heart of the antihypoxic and a number of systemic effects of succinate may lie its proven ability to influence protein HIF-1, which ensures the induction of the genetic apparatus responsible for forming the structural basis for long-term adaptation to hypoxia. The presence of 3-hydroxypyridine in the structure of mexicor facilitates the intracellular penetration of succinic acid and provides for a set of its antioxidant and membranotropic effects and the ability to reduce glutamate excitotoxicity, to modulate the function of receptors, which fundamentally distinguishes these drugs from other medications containing succinic acid (Nikolaev and Bystrova 2008, Okovityy et al. 2012, Evglevsky et al. 2013, Novikov and Levchenkova 2013, Tikhonova et al. 2016).

Ceraxon (citicoline, cytidine-5-diphosphocholine, cytidine diphosphate) after absorption breaks down into choline and cytidine, which easily penetrate the BBB, and after a number of chemical reactions it is converted into cytide-dintriphosphate in brain neurons, gets distributed in the cerebral cortex, white matter, subcortical nuclei, the cerebellum, becoming part of the structural phospholipids of cytoplasmic and mitochondrial membranes. The clinical effects of the drug in conditions of cerebral ischemia are largely related to its antioxidant and reparative properties. Reducing but not suppressing the activity of phospholipase A_2, citicoline restores the content of arachidonic acid of phosphatidyl-choline, which helps stabilize the membrane, resulting in an increased speed of SOD binding to substrates and in improving its activity. By promoting the accumulation of non-enzymatic component of the anti-oxidant system, α-tocopherol, on the cell membrane, citicoline reduces the formation of hydroperoxides of fatty acid and peroxy radicals involved in generating oxidatively modified phospholipids. The choline released from citicoline can get metabolized to glutathione, which is one of the main endogenous antioxidant defense components in the brain, removes hydrogen peroxide and lipid peroxides and prevents the inactivation of glutathione reductase (Solovyova et al. 2016, Putilina 2014, Mendelevich 2016, Adibhatla and Hatcher 2005, Lee et al. 2009, Davies and Guo 2014).

So, by taking into account the literature and the results of our studies given above, there is little doubt about the participation of immune mechanisms in the formation and development of CCI, which made it necessary to use immunomodulators, in particular glutoxim and polyoxidonium, to correct immune disorders (Gusev and Chukanova 2015, Gavrilyuk et al. 2016, Karaulov 2008, Otman et al. 2015, Konoplya et al. 2015).

In a quantitative comparison of the total number of disturbed immunological and metabolic parameters under study, it was found out that in case of CCI-I before treatment 84.4% of the studied parameters were different from the normal values, with that 57.8% of the parameters were found to have II and III degree of disorders requiring correction. After treatment with ceretone and actovegin, 71.1% of the laboratory parameters were found to be changed, with the total of 40.0% with II and III degrees of disorders. After using ceraxon and mexicor, 60.0% of the indicators remained disrupted (40.0% of which with grade II and grade III disorders). After introducing glutoxime into the cexaxon+mexicor regimen, 44.4% of the indicators remained different from the values of healthy donors (28.9% of which with grade II and grade III disorders). The combination of ceraxon, mexicor and polyoxidonium showed great effectiveness, as 24.4% of the parameters were found to be changed, and 15.6% of the parameters had II and III degree of disorders.

The pronounced corrective effects of glutoxim are most likely provided by its selective effect on the functional metabolic activity of monocytes/macrophages, neutrophils, and NK-cells, by increasing or decreasing their activity depending on the initial values. In addition, the drug has pronounced anti-inflammatory, antioxidant and regenerative effects (Spits et al. 2013).

The effects of polyoxidonium, in our studies, primarily are linked to its pronounced immunocorrective action on immunocompetent cells, by increasing or decreasing their activity depending on the initial values, thereby reducing pathological changes in neurons and microglia. Besides, the drug has a pronounced anti-inflammatory, antitoxic, antioxidant, membrane-stabilizing and regenerative actions. (Konoplya et al. 2015, Karaulov 2008, Benarroch 2007, Spits et al. 2013).

Conclusion

1. In case of chronic brain ischemia of I and II stages accompanied by II-degree hypertension, in case of both stages similar changes in the parameters of the system of cytokines and complement were found, the changes being more pronounced with II stage: an increase in the concentration of proinflammatory (TNFα, IL-1β, IL-6, IL-8 , IL-17, IL-18), anti-inflammatory cytokines (IL-4, IL-10, IL-1RA), IFNγ, IL-2 and G-CSF cytokines, reduction of C_3 and C_5-components of the complement, C_1-inhibitor, and an increase in C_{3a} and C_{5a}-components.
2. At chronic ischemia of the brain of I and II stages, no changes were found in the indicators of activity and intensity of circulating neutrophils phagocytosis; in cases of II stage of disease, the activity of oxygen-dependent systems of poly-morphogenic nuclear leukocytes was increased, which can be considered as the most important link in the further development of immune inflammation.
3. In the comparative analysis of the immune status parameters in patients with CCI studied against various treatment regimens used in the study, it was found out that in cases of CCI-I, according to immune and clinical efficacy in ascending order, the drugs under study were arranged in the following order: ceraxon+mexicor ® ceraxon+mexicor+glutoxim ® ceraxon+mexicor+polyoxidonium.
4. In cases of CCI-II, the increasing laboratory efficacy of the combinations used was the following: ceraxon+-

mexicor ® ceraxon+mexicor+polyoxdonium = ceraxon+mexicor+glutoxim.

5. In cases of CCI-II, according to increasing clinical efficacy, the treatment regimens applied were arranged in the following order: by subjective disorders and neurological symptoms: ceraxon+mexicor ® ceraxon+mexicor+glutoxim ® ceraxon+mexicor+polyoxidonium, and by cognitive disorders: ceraxon+mexicor ® ceraxon+mexicor+glutoxim = (on Montreal scale) and ® (on GDR scale) ceraxon+mexicor+polyoxidonium.

Recommendations

1. In the complex pharmacotherapy of chronic ischemia of the brain of I stage accompanied by hypertension, to recommend the use of a combination of ceraxon (1000 mg intravenously, stream infusion, in 24 hours No. 14), mexicor (200 mg after 24 hours, intravenously, stream infusion for 5 minutes, No.14), and polyoxidonium (6 mg, intramuscularly, 8 times (daily for the first 2 days, then every other day).
2. In the complex pharmacotherapy of chronic cerebral ischemia of the brain of II stage accompanied by hypertension, to recommend the use of a combination of ceraxon (1000 mg intravenously, stream infusion, after 24 hours, No. 14), mexicor (200 mg after 24 hours, intravenously, stream infusion for 5 minutes, No. 14) with glutoxim (30 mg in 1 ml of 3% solution, intramuscularly, in 24 hours № 14) or polyoxidonium (6 mg, intramuscularly, 8 times (daily for the first 2 days, then every other day).

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Author contributors

- **Anastasiya A. Shulginova,** PhD in Medicine**,** Assistant Lecturer of the Department of Neurology and Neurosurgery, Kursk State Medical University of the Ministry of Healthcare of Russia, e-mail: snaky292@yandex.ru

- **Alexander I. Konoplya** (corresponding author), Doctor of Medical Sciences, Professor, Honored Scientist of the Russian Federation, Head of the Department of Biological Chemistry, Kursk State Medical University of the Ministry of Healthcare of Russia, e-mail: konoplya51@mail.ru

- **Natalya A. Bystrova,** Doctor of Medical Sciences, Professor of the Department of Biological Chemistry, Kursk State Medical University of the Ministry of Healthcare of Russia, e-mail: bystrova@mail.ru