



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

Anastasiya A. Shulginova<sup>1</sup>, Alexander I. Konoplya<sup>1</sup>, Natalya A. Bystrova<sup>1</sup>

<sup>1</sup> 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](mailto:konoplya51@mail.ru))

Academic editor: Mikhail Korokin ♦ Received 11 July 2018 ♦ Accepted 23 July 2018 ♦ Published 21 August 2018

Citation: Shulginova AA, Konoplya AI, Bystrova NA (2018) Disorders of the immune status in patients with chronic cerebral ischemia; differentiated pharmacological correction. Research Result: Pharmacology and Clinical Pharmacology 4(2): 105–123. <https://doi.org/10.3897/rrpharmacology.4.28304>

## 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<sup>th</sup>-4<sup>th</sup> groups of 12-14 patients) and 52 patients were with CCI II stage (5<sup>th</sup>-7<sup>th</sup> groups of 12-14 patients), aged 50±5, who received the basic pharmacological therapy (enalapril and vinpocetine). The patients of the 2<sup>nd</sup> and 5<sup>th</sup> groups additionally received ceraxon and mexicor, those of the 3<sup>rd</sup> and the 6<sup>th</sup> groups additionally received immunomodulator glutoxim, and those from the 4<sup>th</sup> and 7<sup>th</sup> 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 proinflammatory 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<sup>®</sup> ceraxon+mexicor+glutoxim<sup>®</sup> ceraxon+mexicor+polyoxidonium, and in case of CCI II stage: ceraxon+mexicor<sup>®</sup> 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 pro-

gressing 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: hypertensive 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 crucial 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, IFN $\gamma$ , 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  $\beta$ -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 (1<sup>st</sup> main group) and 52 patients with CCI II stage (2<sup>nd</sup> main group) aged 50 $\pm$ 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 $\pm$ 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 (Brevintin, 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 (TNF $\alpha$ , IL-1 $\beta$ , IL-6, IL-8, IFN $\gamma$ , 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 (Rus-

sia), components of the complement system (C<sub>3</sub>, C<sub>3a</sub>, C<sub>4</sub>, C<sub>5</sub>, C<sub>5a</sub>) and factor H by the diagnostic kit made by Cytokine Ltd. (Russia). The activity of the C<sub>1</sub>-inhibitor was determined by the chromogenic method by its ability to inhibit C<sub>1</sub>-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 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: TNF $\alpha$ , IL-1 $\beta$ , 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 IFN $\gamma$ , 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 TNF $\alpha$ , IL-1 $\beta$ , 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 IFN $\gamma$ , 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<sub>3</sub> and C<sub>5</sub>-components of the complement, C<sub>1</sub>-inhibitor, an increase in C<sub>3a</sub> and C<sub>5a</sub> components was detected, while the level of C<sub>4</sub> 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
<b>Basic pharmacological therapy</b>			
		<b>Berlipril, Cavinton</b>	104
	1	Cereton and Actovegin	12
CCI – I stage	2	Ceraxon and Mexicore	12
	3	Ceracson, Mexicor and Glutoxim	14
	4	Ceracson and Mexicor and Polyoxidonium	14
	1	Cereton and Actovegin	12
CCI – II stage	2	Ceraxon and Mexicore	12
	3	Ceracson, Mexicor and Glutoxim	14
	4	Ceracson and Mexicor and Polyoxidonium	14
	<b>Total</b>		
<b>Donors</b>			22

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

Drug name	Drug dosage regimens
<i>Basic pharmacotherapy</i>	
<p><b>BERLIPRIL</b>  Latin name: Berlipril  International name – Enalapril  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 25.10.00IIIP  Pharmacotherapeutic group: ACE inhibitors</p>	10 mg a day orally, in 24 hours № 14
<p><b>VINPOCETINE</b>  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</p>	10 mg in 200,0 ml 0,9% solution of sodium chloride intravenously, by drop infusion, in 24 hours № 14
<i>Immunomodulators</i>	
<p><b>POLYOXIDONIUM</b>  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</p>	6 mg (intramuscularly), 8 times (daily for the first 2 days, then every second day)
<p><b>GLUTOXIM</b>  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</p>	30 mg in 1 ml of 3% solution, intramuscularly, in 24 hours № 14

Drug name	Drug dosage regimens
<i>Antioxidants/antihypoxants</i>	
<p><b>MEXICORE</b>  Latin name: Mexicor  International non-proprietary name (established name): Ethyl methylhydroxypyridine succinate (Ethylmethylhydroxypyridine succinate)  Brand name: Mexidol<sup>®</sup>, Ethylmethylhydroxypyridine succinate, Mexifin<sup>®</sup>, Mexident<sup>®</sup>Mexicor<sup>®</sup>, 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</p>	<p>200 mg in 24 hours, intramuscularly, stream infusion for 5 min, № 14</p>
<p><b>ACTOVEGIN</b>  Latin name: Actovegin  International non-proprietary name (established name): Deproteinized calf blood haemoderivative  Brand name: Actovegin<sup>®</sup>  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</p>	<p>200 mg of Actovegin (Nycomed Austria GmbH, Austria) in 5 ml, intramuscularly, stream infusion, in 24 hours № 14</p>
<i>Nootropics</i>	
<p><b>CERAXON</b>  Latin name: Ceraxon  International non-proprietary name (established name): Citicoline  Brand name: Ceraxon<sup>®</sup>  Drug form: tablets, intramuscular and intravenous solutions, solution for oral administration  Manufacturer: Ferrer Internacional SA (Spain)  Identification number: JICP-000089-250116  Pharmacotherapeutic group: nootropic</p>	<p>1000 mg intramuscularly, stream infusion, in 24 hours № 14</p>
<p><b>CERETON</b>  Latin name: Cereton  International non-proprietary name (established name): Choline Alfoscerate  Brand name: Cereton<sup>®</sup>  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</p>	<p>1000 mg intramuscularly, stream infusion, in 200,0 ml of 0,9% solution of sodium chloride, in 24 hours № 14</p>

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%) indicators, 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 ( $M \pm m$ )

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

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 ( $M \pm m$ )

Parameters	Units	1	2	3
		Healthy	CCI-I	CCI-II
C <sub>3</sub>	mg/dL	82.2±1.5	66.3±1.7 <sup>*1</sup>	65.1±2.4 <sup>*1</sup>
C <sub>3a</sub>	ng/ml	38.2±2.1	47.1±0.8 <sup>*1</sup>	47.3±1.9 <sup>*1</sup>
C <sub>4</sub>	mg/dL	24.0±0.5	25.1±0.9	25.8±0.7
C <sub>5</sub>	mg/dL	0.1±0.01	0.05±0.006 <sup>*1</sup>	0.05±0.005 <sup>*1</sup>
C <sub>5a</sub>	ng/ml	78.4±3.5	127.4±3.1 <sup>*1</sup>	127.3±4.2 <sup>*1</sup>
C <sub>1</sub> -inh.	ng/ml	288.5±3.0	272.5±2.3 <sup>*1</sup>	274.7±2.4 <sup>*1</sup>
Factor H	ng/ml	39.7±1.0	39.5±1.5	36.8±0.7 <sup>*1,2</sup>

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

Parameters	Units	1	2	3
		Healthy	CCI-I	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 <sup>*1</sup>	11.0±1.2 <sup>*1</sup>
NBT-st	%	25.1±2.4	26.7±1.1	37.5±2.9 <sup>*1,2</sup>
FR	%	17.6±2.3	16.8±1.1	26.5±2.1 <sup>*1,2</sup>
SI	–	3.8±0.6	2.7±0.1 <sup>*1</sup>	3.4±0.3 <sup>*2</sup>

stage, 21 (80.8%) parameters were found to be 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 stage, 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					
	Abs.	%	I		II		III	
			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	2	3
	Healthy	CCI-I	CCI-II
Subjective disorders	0.4±0.02	2.52±0.05 <sup>*1</sup>	2.85±0.06 <sup>*1,2</sup>
Neurological symptoms	0	1.45±0.04 <sup>*1</sup>	2.3±0.04 <sup>*1,2</sup>
Cognitive deterioration on GDR scale	0.15±0.01	1.85±0.06 <sup>*1</sup>	2.75±0.05 <sup>*1,2</sup>
Cognitive deterioration on Monreal scale	27.1±0.3	21.3±0.4 <sup>*1</sup>	18.8±0.7 <sup>*1,2</sup>

mory loss. In case of CCI II stage, 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 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, in case 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 specialized 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- (TNF $\alpha$ , IL-1 $\beta$ , IL-6, IL-8, IL-17 and IL-18) and anti-inflammatory cytokines (IL-4, IL-10 and IL-1RA). The

content of IFN $\gamma$ , 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-1 $\beta$  and IL-1RA normalized, IL-10 increased even more, the level of IFN $\gamma$ , 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 TNF $\alpha$ , 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-1 $\beta$ , IFN $\gamma$ , G-CSF remained unchanged. The use of polyoxidonium, in comparison with the use of ceraxon and mexicor, resulted in the normalized concentration of TNF $\alpha$  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 IFN $\gamma$  remained unchanged (Table 8).

It should be noted that polyoxidonium is more effective than glutoxim, because, when compared, TNF $\alpha$  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<sub>3</sub> and C<sub>5</sub>-components of the complement, C<sub>1</sub>-inhibitor, and an increase in the concentration of C<sub>3a</sub> and C<sub>5a</sub>-components, while the level of C<sub>4</sub> and factor H inhibitor remained within the normal range.

After the treatment, including ceraxon and mexicor, the concentration of C<sub>3</sub> and C<sub>3a</sub> complement components was normalized in patients and the level of C<sub>5</sub> and C<sub>5a</sub> was corrected towards the value of healthy donors. The use of glutamim additionally normalized the content of C<sub>5</sub> complement component and the C<sub>1</sub>-inhibitor. In comparison with glutoxim, polyoxidonium additionally normalized the concentration of C<sub>5a</sub> 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-I				
		Healthy	Before treatment	Ceraxon + Mexicore	Ceraxon + Mexicor + Glutoxime	Ceraxon + Mexicor + Polyoxidonium
IL-1RA	pkg/ml	137.7±1.7	149.3±2.5 <sup>*1</sup>	133.9±2.6 <sup>*2</sup>	139.2±2.7 <sup>*2</sup>	149.2±3.0 <sup>*1-4</sup>
IL-10	pkg/ml	2.7±0.13	3.7±0.1 <sup>*1</sup>	8.4±0.3 <sup>*1,2</sup>	8.9±0.3 <sup>*1,2</sup>	8.6±0.3 <sup>*1,2</sup>
IL-4	pkg/ml	0.4±0.04	3.2±0.08 <sup>*1</sup>	3.2±0.2 <sup>*1</sup>	3.8±0.2 <sup>*1</sup>	4.7±0.5 <sup>*1-3</sup>
IL-8	pkg/ml	1.8±0.06	10.6±0.5 <sup>*1</sup>	6.2±0.3 <sup>*1,2</sup>	3.9±0.1 <sup>*1-3</sup>	2.0±0.06 <sup>*2-4</sup>
IL-17	pkg/ml	8.7±0.2	10.5±0.3 <sup>*1</sup>	9.5±0.2 <sup>*1,2</sup>	8.8±0.2 <sup>*2,3</sup>	9.0±0.3 <sup>*2,3</sup>
IL-18	pkg/ml	47.6±2.1	124.4±4.2 <sup>*1</sup>	94.2±4.5 <sup>*1,2</sup>	55.5±1.9 <sup>*1-3</sup>	60.3±5.7 <sup>*1-3</sup>
TNFα	pkg/ml	2.9±0.07	12.9±0.3 <sup>*1</sup>	8.1±0.4 <sup>*1,2</sup>	4.1±0.3 <sup>*1-3</sup>	3.0±0.1 <sup>*2-4</sup>
IL-1β	pkg/ml	5.3±0.2	12.0±0.4 <sup>*1</sup>	5.4±0.1 <sup>*2</sup>	5.7±0.3 <sup>*2</sup>	5.2±0.2 <sup>*2</sup>
IL-6	pkg/ml	2.4±0.09	13.3±0.6 <sup>*1</sup>	8.6±0.9 <sup>*1,2</sup>	4.3±0.5 <sup>*1-3</sup>	2.9±0.1 <sup>*2-4</sup>
G-CSF	pkg/ml	12.3±1.0	20.3±0.8 <sup>*1</sup>	18.3±1.4 <sup>*1</sup>	16.8±1.0 <sup>*1</sup>	14.0±1.3 <sup>*1-4</sup>
IL-2	pkg/ml	0.14±0.02	6.3±0.3 <sup>*1</sup>	5.9±0.8 <sup>*1</sup>	3.2±0.4 <sup>*1-3</sup>	2.4±0.2 <sup>*1-4</sup>
IFNγ	pkg/ml	15.6±0.3	22.4±0.5 <sup>*1</sup>	22.2±0.9 <sup>*1</sup>	18.3±1.1 <sup>*1</sup>	22.7±1.3 <sup>*1</sup>

**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-I				
		Healthy	Before treatment	Ceraxon + Mexicore	Ceraxon + Mexicor + Glutoxime	Ceraxon + Mexicor + Polyoxidonium
C <sub>3</sub>	mg/dl	82.2±1.5	66.3±1.7 <sup>*1</sup>	83.8±3.9 <sup>*2</sup>	82.4±1.3 <sup>*2</sup>	84.2±4.3 <sup>*2</sup>
C <sub>4</sub>	ng/ml	24.0±0.5	25.1±0.9	23.8±1.4	28.6±1.0	25.5±1.7 <sup>*4</sup>
C <sub>5</sub>	mg/dl	0.1±0.01	0.05±0.006 <sup>*1</sup>	0.07±0.005 <sup>*1,2</sup>	0.09±0.02 <sup>*2</sup>	0.11±0.01 <sup>*2,3</sup>
C <sub>3a</sub>	mg/dl	38.2±2.1	47.1±0.8 <sup>*1</sup>	40.3±2.6 <sup>*2</sup>	36.1±0.9 <sup>*2,3</sup>	44.4±3.2 <sup>*2,4</sup>
C <sub>5a</sub>	ng/ml	78.4±3.5	127.4±3.1 <sup>*1</sup>	91.3±4.9 <sup>*1,2</sup>	101.3±3.8 <sup>*1,2</sup>	77.7±3.2 <sup>*2-4</sup>
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 <sub>1</sub> -inh.	ng/ml	288.5±3.0	272.5±2.3 <sup>*1</sup>	278.8±2.2 <sup>*1</sup>	291.2±2.8 <sup>*2,3</sup>	302.2±4.4 <sup>*1-4</sup>

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 functional 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 symptoms 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-I				
		Healthy	Before treatment	Ceraxon + Mexicore	Ceraxon + Mexicor + Glutoxime	Ceraxon + Mexicor + Polyoxidonium
PI	%	7.5±0.4	9.9±0.1 <sup>*1</sup>	9.9±0.3 <sup>*1</sup>	9.0±0.2 <sup>*1-3</sup>	8.6±0.5 <sup>*1-3</sup>
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 <sup>*1</sup>	2.4±0.3 <sup>*1</sup>	2.5±0.2 <sup>*1</sup>	3.2±0.3 <sup>*2-4</sup>
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-I				
	Healthy	Before treatment	Ceraxon + Mexicore	Ceraxon + Mexicor + Glutoxime	Ceraxon + Mexicor + Polyoxidonium
Subjective disorders	0.4±0.02	2.52±0.05 <sup>*1</sup>	1.72±0.09 <sup>*1,2</sup>	0.94±0.03 <sup>*1-3</sup>	0.5±0.08 <sup>*2,3</sup>
Neurological symptom	0	1.45±0.04 <sup>*1</sup>	1.09±0.08 <sup>*1,2</sup>	1.04±0.04 <sup>*1,2</sup>	0.62±0.02 <sup>*1-4</sup>
Cognitive deterioration on GDR scale	0.15±0.01	1.85±0.06 <sup>*1</sup>	1.41±0.13 <sup>*1,2</sup>	1.33±0.03 <sup>*1,2</sup>	1.09±0.05 <sup>*1-4</sup>
Cognitive deterioration on Monreal scale	27.1±0.3	21.3±0.4 <sup>*1</sup>	24.58±0.6 <sup>*1,2</sup>	26.34±0.46 <sup>*2,3</sup>	26.51±0.57 <sup>*2,3</sup>

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 level of all the cytokines tested: pro-inflammatory (TNF $\alpha$ , IL-1 $\beta$ , IL-6, IL-8, IL-17 and IL-18), anti-inflammatory (IL-4, IL-10 and IL-1RA), IFN $\gamma$ , IL-2 and G-CSF. The treatment, including ceraxon and mexicor, normalized the concentration of IL-1 $\beta$ , 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 IFN $\gamma$  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 TNF $\alpha$ , 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 comparison 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<sub>3</sub> and C<sub>5</sub>-components and inhibitors of the complement system (C<sub>1</sub>-inhibitor and factor H), an increased level of C<sub>3a</sub> and C<sub>5a</sub> components, whereas the C<sub>4</sub> level remained within the normal range. After including ceraxon and mexicor into pharmacotherapy, the concentration of the C<sub>3a</sub>-component of the complement and the factor H inhibitor was normalized, the levels of C<sub>3</sub>, C<sub>5</sub> and C<sub>5a</sub> 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<sub>3</sub> and C<sub>5</sub> components of the complement and the C<sub>1</sub>-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<sub>1</sub> 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				
		Healthy	Before treatment	After treatment		
			Ceraxon + Mexicore	Ceraxon + Mexicor + Glutoxime	Ceraxon + Mexicor + Polyoxidonium	
IL-4	pkg/ml	0.4±0.04	8.0±0.3* <sup>1</sup>	13.8±1.4* <sup>1,2</sup>	14.8±1.7* <sup>1,2</sup>	14.1±1.3* <sup>1,2</sup>
IL-10	pkg/ml	2.7±0.13	3.9±0.1* <sup>1</sup>	4.1±0.1* <sup>1</sup>	6.8±0.3* <sup>1-3</sup>	8.3±0.6* <sup>1-4</sup>
IL-1RA	pkg/ml	137.7±1.7	167.8±1.6* <sup>1</sup>	178.0±3.3* <sup>1,2</sup>	177.2±3.1* <sup>1,2</sup>	196.7±3.8* <sup>1-4</sup>
TNFα	pkg/ml	2.9±0.07	13.5±0.4* <sup>1</sup>	7.8±0.3* <sup>1,2</sup>	5.9±0.3* <sup>1-3</sup>	5.5±0.2* <sup>1-3</sup>
IL-17	pkg/ml	8.7±0.2	22.6±0.9* <sup>1</sup>	15.3±0.7* <sup>1,2</sup>	8.9±0.4* <sup>2,3</sup>	8.3±0.5* <sup>2,3</sup>
IL-18	pkg/ml	47.6±2.1	135.1±5.0* <sup>1</sup>	96.8±5.2* <sup>1,2</sup>	67.4±4.3* <sup>1-3</sup>	52.8±2.7* <sup>1-4</sup>
IL-1β	pkg/ml	5.3±0.2	11.3±0.3* <sup>1</sup>	5.2±0.7* <sup>2</sup>	5.7±0.2* <sup>2</sup>	5.4±0.2* <sup>2</sup>
IL-6	pkg/ml	2.4±0.09	14.2±0.5* <sup>1</sup>	10.5±0.7* <sup>1,2</sup>	7.4±0.9* <sup>1-3</sup>	3.9±0.07* <sup>1-4</sup>
IL-8	pkg/ml	1.8±0.06	16.2±0.7* <sup>1</sup>	11.0±0.8* <sup>1,2</sup>	8.3±0.9* <sup>1-3</sup>	2.5±0.05* <sup>1-4</sup>
IFNγ	pkg/ml	15.6±0.3	23.6±0.7* <sup>1</sup>	28.6±0.8* <sup>1,2</sup>	27.4±1.3* <sup>1,2</sup>	35.8±1.9* <sup>1,2</sup>
IL-2	pkg/ml	0.14±0.02	6.8±0.4* <sup>1</sup>	7.8±1.3* <sup>1</sup>	7.4±0.8* <sup>1</sup>	2.7±0.8* <sup>1-4</sup>
G-CSF	pkg/ml	12.3±1.0	23.6±1.1* <sup>1</sup>	20.2±2.2* <sup>1,2</sup>	15.2±2.1* <sup>2,3</sup>	14.3±1.0* <sup>2,3</sup>

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

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 glutoximomic polyoxidonium ( $M \pm m$ )

Parameters	Unit	1	2	3	4	5
		CCI-II				
		Healthy	Before treatment	After 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 <sup>*1</sup>	12.1±1.3 <sup>*1</sup>	8.4±0.9 <sup>*2,3</sup>	8.1±0.6 <sup>*2,3</sup>
NBT-st	%	25.1±2.4	37.5±2.9 <sup>*1</sup>	39.6±4.0 <sup>*1</sup>	29.5±1.2 <sup>*1-3</sup>	29.6±2.2 <sup>*1-3</sup>
FRN	%	17.6±2.3	26.5±2.1 <sup>*1</sup>	27.4±4.1 <sup>*1</sup>	21.1±1.7 <sup>*1-3</sup>	21.5±2.3 <sup>*1-3</sup>
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 ( $M \pm m$ )

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

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 ceretone 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					
	total	%	I		II		III	
			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-II

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 (TNF $\alpha$ , 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, Spencer et al. 2014).

TNF $\alpha$ , the primary mediator of inflammation involved in the pathogenesis of most infectious and immunopathological diseases, coordinates an inflammatory response and the cytokine cascade (IL-1 $\beta$ , 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 sterile inflammation, participates in the transformation of local inflammation into a systemic inflammation, stimulates the synthesis of IL-6, TNF $\alpha$ , IL-12, IL-8, IL-23, IFN $\gamma$ , 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-1 $\beta$  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, TNF $\alpha$ , IFN $\gamma$ , 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 IFN $\gamma$  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 IFN $\gamma$  (effector of cellular immune response of inflammatory type) and prolonged retention of an increased ratio IFN $\gamma$ /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 IFN $\gamma$ -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-stimulating 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<sub>3</sub> and C<sub>5</sub> with an increase in the levels of fragments C<sub>3a</sub> and C<sub>5a</sub> 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 im-

munopathology 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 Kaluzhin 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 cytidine diphosphate 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<sub>2</sub>, 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,  $\alpha$ -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, Gavriilyuk 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 ceraxon+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 (TNF $\alpha$ , IL-1 $\beta$ , IL-6, IL-8, IL-17, IL-18), anti-inflammatory cytokines (IL-4, IL-10, IL-1RA), IFN $\gamma$ , IL-2 and G-CSF cytokines, reduction of C<sub>3</sub> and C<sub>5</sub>-components of the complement, C<sub>1</sub>-inhibitor, and an increase in C<sub>3a</sub> and C<sub>5a</sub>-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<sup>®</sup> ceraxon+mexicor+glutoxim<sup>®</sup> ceraxon+mexicor+polyoxidonium.
4. In cases of CCI-II, the increasing laboratory efficacy of the combinations used was the following: ceraxon+

mexicor<sup>®</sup> ceraxon+mexicor+polyoxdonium = ceraxon+mexicor+glutoxim.

- 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<sup>®</sup> ceraxon+mexicor+glutoxim<sup>®</sup> ceraxon+mexicor+polyoxidonium, and by cognitive disorders: ceraxon+mexicor<sup>®</sup> ceraxon+mexicor+glutoxim = (on Montreal scale) and<sup>®</sup> (on GDR scale) ceraxon+mexicor+polyoxidonium.

## Recommendations

- 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).

- 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).

## References

- Adibhatla RM, Hatcher JF (2005) Cytidine 5'-diphosphocholine (CDP-choline) in stroke and other CNS disorders. *Neurochemical Research* 30(1): 15–23. <https://doi.org/10.1007/s11064-004-9681-8> [PubMed]
- Adibhatla RM, Hatcher JF, Larsen EC, et al. (2006) CDP-choline significantly restores phosphatidylcholine levels by differentially affecting phospholipase A2 and CTP: Phosphocholine cytidyltransferase after stroke. *Journal of Biological Chemistry* 281(10): 6718–6725. <https://doi.org/10.1074/jbc.M512112200> [PubMed]
- Benarroch E (2007) Neurovascular unit dysfunction: a vascular component of Alzheimer disease? *Neurology* 68(20): 1730–1732. <https://doi.org/10.1212/01.wnl.0000264502.92649.ab> [PubMed]
- Boyadzhyan AS, Tsakanova GV, Zhangaryan LG, et al. (2010) Involving a lectin cascade of complement in a postischemic inflammatory response. *Cytokines and inflammation [Tsitokiny i vospalenie]* 9(33): 35–39. [in Russian]
- Chen CJ, Kono H, Golenbock D, et al. (2007) Identification of a key pathway required for the sterile inflammatory response triggered by dying cells. *Nature Medicine* 13(7): 851–856. <https://doi.org/10.1038/mi.2009.100> [PubMed]
- Chen S, Shimada K, Zhang W (2010) IL-17A Is Proatherogenic in High-Fat Diet-Induced and *Chlamydia pneumoniae* Infection-Accelerated Atherosclerosis in Mice. *Journal of Immunology* 185(9): 5619–5627. <https://doi.org/10.4049/jimmunol.1001879> [PubMed]
- Chukanova EI, Chukanov AS (2014) The use of antioxidant drugs in the complex pathogenetic therapy of vascular cognitive disorders. *Russian Medical Journal [Russkiy meditsinskiy zhurnal]* 3(10): 759–763. [in Russian]
- Zonneveld HI, Goos JD, Wätjes MP, Prins ND, Scheltens P, van der Flier WM, Kuijjer JP, Muller M, Barkhof F (2006) Prevalence and severity of microbleeds in a memory clinic setting. *Neurology* 66(9): 1356–1360. <https://doi.org/10.1212/WNL.0000000000000150> [PubMed]
- Damulin IV, Ekushev EV (2014) Dementia due to the damage of small cerebral vessels: modern concepts of pathogenesis and therapy. *Neurology, Neuropsychiatry, Psychosomatics [Nevrologiya, neiropsikhiatriya, psikhosomatika]* 4: 94–100. [in Russian]
- Davies SS, Guo L (2014) Lipid peroxidation generates biologically active phospholipids including oxidatively N-modified phospholipids. *Chemistry and Physics of Lipids* 181: 1–33. <https://doi.org/10.1016/j.chemphyslip.2014.03.002> [PubMed]
- Evglevsky AA, Ryzhkova GF, Evglevskaya EP, et al. (2013) Biological role and metabolic activity of succinic acid. *Bulletin of the Kursk State Agricultural Academy [Vestnik Kurskoy gosudarstvennoy sel'skokhozyaystvennoy akademii]* 15(1): 67–69. [in Russian]
- Farrall AJ, Wardlaw JM (2009) Blood-brain barrier: ageing and microvascular disease – systematic review and meta-analysis. *Neurobiology of Aging* 30(3): 337–352. <https://doi.org/10.1016/j.neurobiolaging.2007.07.015> [PubMed]
- Folstein MF, Folstein SE, Hugh PR (1975) “Mini-mental state” – A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research* 12(3): 189–198. [https://doi.org/10.1016/0022-3956\(75\)90026-6](https://doi.org/10.1016/0022-3956(75)90026-6) [PubMed]
- Gavriluk EV, Konoplya AI, Karaulov AV (2016) The role of immune disorders in the pathogenesis of arterial hypertension. *Immunology [Immunologiya]* 37(1): 29–34. [in Russian]
- Girouard H, Iadecola C (2006) Neurovascular coupling in the normal brain and in hypertension, stroke and alzheimer disease. *Journal of Applied Physiology* 100(1): 328–335. <https://doi.org/10.1152/jap-physiol.00966.2005> [PubMed]
- Gusev EI, Chukanova AS (2015). Modern pathogenetic aspects of the formation of chronic cerebral ischemia. *Journal of Neurology and Psychiatry [Zhurnal nevrologii i psikiatrii]* 3: 4–8. [in Russian]
- Jellinger KA, Attems J (2010) Prevalence of dementia disorders in the oldest-old: an autopsy study. *Acta Neuropathol* 119(4): 421–433. <https://doi.org/10.1007/s00401-010-0654-5>. [PubMed]
- Kadykov AS, Manvelov LS, Shakhparonova NV (2014) Chronic vascular diseases of the brain: dyscirculatory encephalopathy. A guide for doctors (3<sup>rd</sup> edn), Revised [Khronicheskie sosudistye zabolovaniya golovnogo mozga: distsirkulyatornaya entsefalopatiya]. GEOTAR-Media, Moscow, 123 pp. [Full text]
- Kamchatnov PR, Salnikova GS, Mikhailova NA (2016) Chronic disorders of cerebral circulation and the possibility of their pharmacological correction. *Journal of Neurology and Psychiatry [Zhurnal nevrologii i psikiatrii]* 6: 72–75. [in Russian]



- Karaulov AV (2008) Polyoxidonium in clinical practice – Therapy – Surgery – Gynecology – Urology – Oncology [Polioksidoniy v klinicheskoy praktike. Terapiya. Khirurgiya. Ginekologiya. Urologiya. Onkologiya]. GEOTAR-Media, Moscow, 136 pp. [in Russian]
- Karaulov AV, Afanasyev SS, Aleshkin VA, et al. (2015) Microflora, colonization mucosal resistance and mucosal immunity. *Immunology [Immunologiya]* 5: 290–295. [in Russian]
- Karaulov AV, Kalyuzhin OV (2013) Immunotherapy of infectious diseases: problems and prospects. *Therapeutic archive [Terapevticheskiy arkhiv]* 85(11): 100–108. [in Russian]
- Ketlinsky SA, Simbirtsev AS (2008) Cytokines. [Tsitokiny]. Publishing house “Folio”, St. Petersburg, 552 pp. [in Russian]
- Khaden SA, Gaffen SL, Kolls JK (2009) Th17 cells at the crossroads of innate and adaptive immunity against infectious diseases at the mucosa. *Mucosal Immunol* 2(5): 403–411. <https://doi.org/10.1038/mi.2009.100> [PubMed]
- Khaitov RM, Ignatieva GA, Sidorovich IG (2010) Immunology. Norm and pathology. [Immunologiya. Norma i patologiya] Publishing house “Medicine”, Moscow, 752 pp. [in Russian]
- Konoplya AI, Gavrilyuk VP, Loktionov AL (2015) Clinical experience of the joint use of immunomodulators, antioxidants and membranoprotectors in clinical practice [Klinicheskiy opyt sovместnogo ispol'zovaniya immunomodulyatorov, antioksidantov i membranoprotektorov v klinicheskoy praktike]. Publishing house of the Municipal Unitary Enterprise “Kursk city printing house”, Kursk, 160 pp. [in Russian]
- Konoplya AI, Laskov VB, Shulginova AA (2015) Immune and oxidant disorders in patients with chronic cerebral ischemia and their correction. *Journal of Neurology and Psychiatry [Zhurnal neurologii i psikiatrii]* 11: 28–32. [in Russian]
- Konoplya AI, Lazarenko VA, Loktionov AL (2013) Interrelation of immunometabolic and erythrocyte disorders with etiology of acute pancreatitis. [Vzaimosvjaz' immunometabolicheskikh i eritrotsitarnykh narusheniy s etiologiyey ostrogo pankreatita]. Publishing house of the Kursk State Medical University of the Ministry of Health of Russia, Kursk, 162 pp. [in Russian]
- Lee HJ, Kang JS, Kim YL (2009) Citicoline protects against cognitive impairment in a rat model of chronic cerebral hypoperfusion. *Journal of Clinical Neurology* 5(1): 33–38. <https://doi.org/10.3988/jcn.2009.5.2.104> [PubMed]
- Levin OS (2012) Dyscirculatory encephalopathy: an anachronism or a clinical reality? *Modern therapy in psychiatry and neurology [Sovremennaya terapiya v psikiatrii i neurologii]* 3: 40–46. [in Russian]
- Levin OS, Barantsevich ER, Belskaya GN, et al. (2014) Effectiveness of combined vasobral preparation in dyscirculatory encephalopathy. *Journal of Neurology and Psychiatry [Zhurnal neurologii i psikiatrii]* 10: 25–29. [in Russian]
- Libby P, Ridker PM, Hansson GK (2011) Progress and challenges in translating the biology of atherosclerosis. *Nature* 473(7347): 317–325. <https://doi.org/10.1038/nature10146> [PubMed]
- Litvinenko IV, Vorobiev SV, Lobzin VY, Lupanov IA (2013) Possibilities of pharmacological modulation of the cerebral glutamatergic system in the treatment of vascular cognitive impairments. *Journal of Neurology and Psychiatry [Zhurnal neurologii i psikiatrii]* 9: 29–35. [in Russian]
- Loktionov AL, Konoplya AI, Lunev MA, Karaulov AV (2015) Immune and oxidant disorders in the pathogenesis of inflammatory periodontal diseases. *Immunology [Immunologiya]* 36(5): 319–328. [in Russian]
- Lukens JR, Gross JM, Kanneganti TD (2012) IL-1 family cytokines trigger sterile inflammatory disease. *Frontiers in Immunology* 3: 315. <https://doi.org/10.3389/fimmu.2012.00315> [PubMed]
- Mendelevich EG (2016) Chronic cerebral vascular insufficiency: clinical and neuroimaging parameters, risk factors and neuroprotective therapy *Russian Medical Journal [Russkiy meditsinskiy zhurnal]* 7: 424–428. [in Russian]
- Menshikov IV, Makarova MI, Bulatova NI (2010) Autoimmune reactions in the pathogenesis of atherosclerosis. *Immunology [Immunologiya]* 5: 242–246. [in Russian]
- Mitra S, Khaidakov MJ, et al. (2011) Prior exposure to oxidized low-density lipoprotein limits apoptosis in subsequent generations of endothelial cells by altering promoter methylation. *American Journal of Physiology – Heart and Circulatory Physiology* 301(2): H506–13. <https://doi.org/10.1152/ajpheart.00252.2011> [PubMed]
- Nelson PT, Head E, Schmitt FA, et al. (2011) Alzheimer’s disease is not “brain aging”: neuropathological, genetic, and epidemiological human studies. *Acta Neuropathologica* 121(5): 571–587. <https://doi.org/10.1007/s00401-011-0826-y> [PubMed]
- Nikolaev SB, Bystrova NA (2008) Immunomodulating effects of mexicor in conditions of hypoxia. *Bulletin of new medical technologies [Vestnik novykh meditsinskikh tekhnologiy]* 15(1): 207–210. [in Russian]
- Novikov VE, Levchenkova OS (2013) New directions of searching for drugs with antihypoxic activity and targets for their action. *Experimental and Clinical Pharmacology [Eksperimental'naya i klinicheskaya farmakologiya]* 76(5): 47. [in Russian]
- O'Brien JT, Erkinjuntti T, Reisberg B, et al. (2003) Vascular cognitive impairment. *Lancet Neurology* 2 (2): 89–98. [https://doi.org/10.1016/S1474-4422\(03\)00305-3](https://doi.org/10.1016/S1474-4422(03)00305-3) [PubMed]
- Okovityy SV, Zaplutanov VA, Smagina AN, Sukhanov DS (2012) Antihypoxants in modern clinical practice. *Clinical medicine [Klinicheskaya meditsina]* 9: 63–68. [in Russian]
- Otman IN, Zozulya SA, Sarmanova ZV, Klushnik TP (2015) Inflammatory and autoimmune reactions in various forms of impaired functioning of the nervous system. *Pathological physiology and experimental therapy [Patologicheskaya fiziologiya i yeksperimental'naya terapiya]* 59(3): 81–88. [in Russian]
- Ovesgharan S, Hachinski V (2010) Hypertension, executive dysfunction, and progression to dementia: the canadian study of health and aging. *Archives of Neurology* 67(2): 187–192. <https://doi.org/10.1001/archneurol.2009.312> [PubMed]
- Pantoni L, Poggesi A, Inzitari D (2007) The relation between white-matter lesions and cognition. *Current Opinion in Neurology* 20 (4): 390–397. <https://doi.org/10.1097/WCO.0b013e328172d661> [PubMed]
- Pigarevskyy PV, Maltseva SV, Snegova VA, Davydova NG (2014) The role of interleukin-18 in the destabilization of atheroma in humans. *Bulletin of Experimental Biology and Medicine [Bjulleten' eksperimental'noy biologii i meditsiny]* 157(1): 796–800. [in Russian]
- Putilina MV (2014) The role of arterial hypertension in the development of chronic cerebral circulatory disorders. *Journal of Neurology and Psychiatry [Zhurnal neurologii i psikiatrii]* 9: 124–128. [in Russian]
- Putilina MV (2016) Combining the use of neuroprotectors in the therapy of cerebrovascular diseases. *Journal of Neurology and Psychiatry [Zhurnal neurologii i psikiatrii]* 11: 58–63. [in Russian]

- Pyokhova KA, Mikhin VP, Gavrilyuk EV, Konoplya AI (2012) Immunometabolic disorders in hypertensive disease of different severity. *Bulletin of new medical technologies [Vestnik novykh meditsinskikh tekhnologiy]* 19(1): 172–173. [in Russian]
- Roger VL, Go AS, Lloyd-Jones DM, et al. (2012) Executive summary: heart disease and stroke statistics – 2012 update: a report from the American Heart Association. *Circulation* 125(1): 188–197. <https://doi.org/10.1161/CIR.0b013e3182456d46> [PubMed]
- Roman GC, Erkinjuntti T, Wallin A, et al. (2002) Subcortical ischemic vascular dementia. *Lancet Neurology* 1 (7): 426–436. [https://doi.org/10.1016/S1474-4422\(02\)00190-4](https://doi.org/10.1016/S1474-4422(02)00190-4) [PubMed]
- Schmidtke K, Hull M (2005) Cerebral small vessel disease: how does it progress? *Journal of the Neurological Sciences* 229(230): 13–20. <https://doi.org/10.1016/j.jns.2004.11.048> [PubMed]
- Serebryanaya NB, Lobzin SV, Kula II, Ischenko AM (2015) The state of the complement system in the first attack of demyelinating diseases – multiple sclerosis and clinically isolated syndrome. *Cytokines and inflammation [Tsitokiny i vospalenie]* 14(3): 42–46. [in Russian]
- Shulginova AA, Laskov VB, Bystrova NA (2015) Dynamics of the clinical picture and immunometabolic indices in cases of chronic cerebral ischemia with combined protracted treatment using of nootropic and antioxidant drugs. *Kursk Scientific and Practical Bulletin “The Man and His Health” [Kurskiy nauchno-prakticheskiy vestnik “Chelovek i ego zdorov’e”]* 1: 65–71. [in Russian]
- Shulginova AA, Voronina EY, Konoplya AI, Loktionov AL (2014) The system of complement and immunoglobulins in patients with discirculatory encephalopathy. *System analysis and management in biomedical systems [Sistemnyy analiz i upravlenie v biomeditsinskikh sistemakh]* 13 (2): 466–471. [in Russian]
- Simbirtsev AS (2004) Cytokines: Classification and biological functions. *Cytokines and inflammation [Tsitokiny i vospalenie]* 3(2): 16–22. [in Russian]
- Skvortsova VI, Stakhovskaya LV, Bodykhov MK (2014) Some indicators of systemic hemodynamics in predicting the lethal outcome in patients with acute stroke. *Bulletin of Russian Federal Service for Supervision in Healthcare [Vestnik Roszdravnadzora]* 1: 37–43. [in Russian]
- Sologub TV, Osinovets OYu (2013) Immunomodulators in the complex treatment of acute respiratory viral infection: the possibility of using Galavit drug. *Russian Medical Journal [Russkiy medicinskiy zhurnal]* 3: 144–146. [in Russian]
- Solovyova AG, Peretyagin SP, Didenko NV, Dudar AI (2016) Changes in pro- and anti-oxidant balance of blood under chronic exposure to singlet oxygen in the experiment. *Bulletin of new medical technologies [Vestnik novykh meditsinskikh tekhnologiy]* 23(2): 50–55. [in Russian]
- Spencer JD, Schwaderer AL, Becknell B, et al. (2014) The innate immune response during urinary tract infection and pyelonephritis. *Pediatric nephrology (Berlin, Germany)* 29(7): 1139–1149. <https://doi.org/10.1007/s00467-013-2513-9> [PubMed]
- Spits H, Artis D, Colonna M, et al. (2013) Innate lymphoid cells – a proposal for a uniform nomenclature. *Nature Reviews Immunology* 13(2): 145–149. <https://doi.org/10.1038/nri3365> [PubMed]
- Suslina ZA, Rumyantseva SA, Tanashyan MM, et al. (2011) Complex correction of chronic cerebral ischemia. *Journal of Neurology and Psychiatry [Zhurnal neurologii i psikiatrii]* 3: 25–30. [in Russian]
- Tabeeva GR (2015) Clinical phenomenology, mechanisms of formation and pathogenetic therapy of early manifestations of chronic cerebral ischemia. *Clinical pharmacology and therapy [Klinicheskaya farmakologiya i terapiya]* 24: 81–87. [in Russian]
- Tanashyan MM, Lagoda OV, Antonova KV, Konovalov RN (2016) Chronic cerebrovascular diseases and metabolic syndrome: approaches to pathogenetic therapy of cognitive impairments. *Journal of Neurology and Psychiatry [Zhurnal neurologii i psikiatrii]* 9: 106–110. [in Russian]
- Tikhonova EO, Lyapina EP, Shuldyakov AA, Satarova SA (2016) Use of preparations containing succinate in the clinic of infectious diseases. *Therapeutic archive [Terapevticheskiy arkhiv]* 88 (11): 121–127. [in Russian]
- Turmova EP, Markelova EV, Silaev AA, et al. (2014) Features of cytokine status in patients with atherosclerosis. *Medical Immunology [Meditsinskaya immuno-logiya]* 16(4): 323–331. [in Russian]
- Vorobyova EN, Schumacher GI, Khoreva MA, Osipova IV (2010) Endothelial dysfunction – a key link in the pathogenesis of atherosclerosis. *Russian Cardiological Journal [Rossiiskiy kardiologicheskii zhurnal]* 2: 84–91. [in Russian]
- Voronina EYu, Laskov VB, Shulginova AA, Konoplya AI (2014) Cytokine spectrum in patients with chronic cerebral ischemia (discirculatory encephalopathy) and correction of its disorders. *Kursk scientific and practical bulletin “The Man and His Health” [Kurskiy nauchno-prakticheskiy vestnik “Chelovek i ego zdorov’e”]* 1: 52–58. [in Russian]
- Wancata J, Freidl M, Krautgartner M, et al. (2008) Gender aspects of parents’ needs of schizophrenia patients. *Social Psychiatry and Psychiatric Epidemiology* 43(12): 968–974. <https://doi.org/10.1007/s00127-008-0391-4> [PubMed]
- Xu WL, Qiu CX, Wahlin A, et al. (2004) Diabetes mellitus and risk of dementia in the Kungsholmen project: a 6-year follow-up study. *Neurology* 63(7): 1181–1186. <https://doi.org/10.1212/01.WNL.0000140291.86406.D1> [PubMed]
- Yarilin AA (2010) *Immunology [Immunologiya]*. Publishing house GEOTAR-Media, Moscow, 749 pp. [in Russian]
- Zakharov VV, Vakhnina NV, Gromova DO, Tarapovskaya AV (2016) Chronic insufficiency of cerebral circulation: a description of the clinical case. *Therapeutic Archive [Terapevticheskiy arkhiv]* 4: 93–99. [in Russian]
- Zakharova MN, Illarionkin SN, Lysogorskaya EV, et al. (2014) *Neurology*. In: Gusev EI (Ed.) *National Guideline [Natsional’noe rukovodstvo]*. GEOTAR-Media, Moscow, 688 pp. [in Russian]
- Zemskov AM, Zemskov VM, Zoloyedov VI (2013) *Unorthodox immunology [Neortodoksal’na ya immunologiya]*. “Triada-X”, Moscow, 222 pp. [in Russian]
- Zurochka AV, Davydova EV, Altman DS (2013) Cytokine control of blood-brain barrier regulation and levels of neuron-specific markers of damage to nerve tissue in patients with early forms of chronic cerebral ischemia. *Russian Immunological Journal [Rossiiskiy immunologicheskii zhurnal]* 7(4): 451–455. [in Russian]

## 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](mailto: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](mailto: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](mailto:bystrova@mail.ru)