ijlpr 2022; doi 10.22376/ijpbs/lpr.2022.12.6.SP23.L57-62

International Journal of Life science and Pharma Research

ISSN 2250-0480

Research Article

Chronic Cerebral Ischaemia Stages I-Ii of the Disease: Immune and Metabolic Disorders

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Abstract: Due to the increase in average-expectancy life in most developed countries and the environmental deterioration, there has been an increase in cerebrovascular and neurodegenerative diseases. Hence, this study attempts to analyze the chronic Cerebral Ischaemia Stages I-Ii of the disease, immune and metabolic disorders. To fulfil the study's aim, seventy-five patients of the neurological department of "Kursk Regional Clinical Hospital" suffering from CCI in presence of hypertension, where 32 patients were with the stage I (1st main group) and 43 - with the stage II (2nd main group) at the age of 50 ± 5 years old are examined. In patients with chronic cerebral ischemia (CCI) stages I and II in presence of hypertension, among the 28 studied parameters of the immune and metabolic status of the blood plasma in addition to the content of the C4 component and the complement factor H inhibitor, 92,9% of the indicators were changed from the values of healthy donors at the start of treatment, in the patients with both stages of the disease 73,1% of these parameters turned out to be the same in magnitude and direction of changes, and 26,9% were identical in direction. The data obtained indicate the presence of immune inflammation, oxidative stress, endothelial dysfunction, and activation of lipid peroxidation in patients with CCI. The performed standard pharmacotherapy did not normalize 61,5% of the studied laboratory immune and metabolic indicators changed prior to the treatment in patients with CCI stage I and 76,9% of those with stage II, which, in its turn, makes necessary the correction of immunometabolic disorders at an early stage of the disease, studies of various combinations of preparations with antioxidant, nootropic, metabolic action in complex pharmacotherapy, and the introduction of immunomodulators into the accepted therapeutic regimens are necessary as well.

Keywords: Blood Plasma, Chronic Cerebral Ischemia, Hypertension, Immune And Metabolic Disorders.

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Received On 04 August 2022

Revised On 09 September 2022

Accepted On 16 September 2022

Published On 20 September 2022

Funding This research did not receive any specific grant from any funding agencies in the public, commercial or not for profit sectors.

Citation Shulginova Anastasiya Aleksandrovna , Litvinova Ekaterina Sergeevna , Bushmina Olga Nikolaevna and Dudka Viktor Tarasovich , Chronic Cerebral Ischaemia Stages I-Ii of the Disease: Immune And Metabolic Disorders.(2022).Int. J. Life Sci. Pharma Res.12(6.SP23), L57-62 http://dx.doi.org/10.22376/ijpbs/lpr.2022.12.6.SP23.L57-62

1. INTRODUCTION

Nowadays in the Russian Federation the number of people aged 65 and older is about 20%. Diseases of the nervous system are included in the five classes of the most common diseases for people in the older age group[1-3]. The most common in clinical practice of senior patients are: Parkinson's disease, Alzheimer's, vascular diseases of the brain. The latter can include both acute and chronic forms of cerebrovascular accident. Chronic disorders of blood flow in the brain (chronic cerebral ischemia - CCI) are slow and progressively result in diffuse or focal disorders of symptoms and signs with a high risk of acute cerebrovascular accident [2-6]. CCI provoked by arterial hypertension (AH) activates microglial cells, resulting in the development of a local inflammatory response with the participation of cytokines[7,8]. Important target-cells for the latter are astrocytes, which are involved, among other things, in a decrease in the body's immune tolerance to the brain tissues, and this, along with the processes of endothelial dysfunction and apoptosis, causes the damage to the brain tissues. The immune inflammation and impaired lipid metabolism results in an irreversible damage to phospholipid membrane complexes and a destructive process in the neuroglia, so all of the above are the reasons for the clinical manifestations of CCI [9-11]. At the same time, the literature does not sufficiently cover the issues on the study of factors that ensure the interaction of various indicated pathogenic mechanisms of CCI onset and development at various stages of the disease, knowledge of which will allow for profile pathogenic pharmacorrection[12-15]. Due to an increase in cerebrovascular and neurodegenerative diseases, especially in developed countries, this study makes an attempts to analyze the chronic Cerebral Ischaemia Stages I-Ii of the disease, immune and metabolic disorders. The main aim of the study is the determination of immune and metabolic disorders prior to and after standard treatment in patients with CCI, depending on the stage of the disease

2. MATERIALS AND METHODS

We have examined 75 patients of the neurological department of "Kursk Regional Clinical Hospital" suffering from CCI in presence of hypertension, where 32 patients were with the stage I (1st main group) and 43 - with the stage II (2nd main group) at the age of 50 ± 5 years old. In addition, we have studied immunological and metabolic parameters in plasma samples and erythrocytes of peripheral blood from 15 healthy donors (52 ± 2 years old) who made a control group; the obtained results are accepted as a conditional norm. The inclusion criteria for the main group are as follows: male; CCI in presence of hypertension stage II, diagnosed 5 or more years ago in accordance with the recommendations of the World Health Organization and the International Society for AH (ISH, 1999)[2,4]. All the patients underwent a comprehensive clinical and instrumental examination according to generally accepted standards[5-10], thereby in all cases the diagnosis of CCI stages I and II was verified. The examination methods included clinical assessment of neurological status[4,5]; the degree of cognitive disorders was assessed using the Global Deterioration Rating and the Montreal Cognitive Assessment[7,9], MRI of the brain[16,17]. The patients of the main groups received complex basic therapy (the inhibitor of angiotensin-converting enzyme enalapril and vasoactive preparation vinpocetinum (Cavinton) and additional therapy (nootropic drug Ceraxon and antioxidant drug - Mexicor)[18,19]. The assessment of clinical and laboratory data[4,7,20] and neurological status in the main and control groups was carried out at the beginning of the treatment and in 2 weeks after its end. Erythrocytes and plasma were obtained from 10 ml of heparinized blood, for this purpose it was twice defecated in 10 mM Na-phosphate buffer (pH = 7,4) containing 0,9% sodium chloride and 3% dextran T-500 for 30 minutes at 37° C. Then the blood was centrifuged, plasma was obtained, and the erythrocyte mass was subjected to additional purification on a chromatographic column through HBS-cellulose[5-7]. The intensity of lipid peroxidation (LPO)[2,11,21] processes was assessed by conventional methods according to the content of degradation products of polyunsaturated fatty acids - derivatives of thiobarbituric acid (malonyldialdehyde - MDA and acyl hydroperoxides - AHP) in blood plasma and erythrocytes[6,9,13]. The state of the antioxidant system[7,22] was assessed by direct/ competitive solid-phase enzyme immunoassay (EIA) with detection of reaction products in the wavelength ranging from 405 to 630 by means of ready-made commercial kits: superoxide dismutase (SOD) activity by "Bender Medsystems" (Austria), catalase by "Cayman Chemical" (the USA) and the level of neopterin by "IBL" (Germany)[13-17]. The concentration of stable nitric oxide metabolites (total NO, SM_{NO})[23-25] was detected using two analytical operations: measurement of endogenous nitrite and conversion of nitrate into nitrite using nitrite reductase, followed by measurement of total nitrite[17,26] by the absorption of azo dye in Griess reaction at a wavelength 540 nm using a kit for EIA by "R&D" (England)[14,18,19]. In addition, the level of C-reactive protein (CRP)[2,14,27] by "Vector-Best" (Russia) and endothelin-1 by 'Biomedica' (Slovakia) were determined in blood plasma. The content of cytokines, complement components and their inhibitors was determined in the blood plasma. Cytokines (TNFα, IL-1β, IL-17, IFNγ, IL-10, IL-1RA) were detected by solid-phase EIA using the kits from ZAO "Vector-Best" (Russia), components of the complement system (C_3, C_{3a}, C_4, C_5, C_{5a}) and factor H - with the diagnostic kit from "Tsytokin" LLC (Russia) by two principles: the hemolytic method for recording the activation of CS and the EIA method for detecting the terminal complex revealed by specific antibodies. The activity of C_1-inhibitor was determined by the chromogenic method according to its ability to inhibit C_1-esterase. All the EIA results were recorded using a microplate photometer "Sunrise", Tecan (Austria)[28-31].

3. STATISTICAL ANALYSIS

Statistical analysis of the research results was carried out in accordance with the generally accepted criteria for variable-based statistical analysis where the calculation of mean values (M), mean deviation (m) was performed using the software package Microsoft Excel 2010. The significance of differences was assessed by Mann-Whitney U-test. Differences with $p < 0.05$ were considered statistically significant. The ethics committee of Kursk State Medical University confirmed that there is no ethical issue in this study.

4. RESULTS AND DISCUSSION

Prior to the treatment in the blood plasma of patients suffering from CCI stage I there was an increase in the concentration of anti-inflammatory cytokines: TNFα, IL-1β, IFNγ and IL-17 by 4,5, 2,2, 1,4 and 1,2 times respectively, anti-inflammatory cytokines: IL-10 and IL-1RA by 1,4 and 1,1

times respectively, a decrease in the content of C_3 and C_5 components of complement, C_1 inhibitor by 1,2, 1,9 and 1,1 times respectively, an increase in C_{3a} and C_{5a} by 1,2 and 1,6 times, respectively, and the level of C_4-component and factor H inhibitor remained within normal limits. After the treatment the concentrations of IL-1β, IL-17, IL-1RA, C_3 and C_{3a}-components normalized, the content of TNFα, C_5 and C_{5a} was corrected towards the values of healthy donors, the level of IFNγ and C_1-inhibitor did not change, and IL-10 increased to an even greater extent (Table 1).

Table 1. Immunological Indicators of Blood Plasma in Patients with CCI Stage I and II (M ± m)

Indicators	units of measurement	1	2	3	4	5
			CCI-1		CCI-2	
		Healthy	Prior to the treatment	After the treatment	Prior to the treatment	After the treatment
TNFα	pg/ml	2,9±0,07	13,0±0,41*1	8,1±0,35*1,2	11,4±0,42*1,2	7,8±0,29*1,4
IL-1β	pg/ml	5,3±0,2	11,9±0,31*1	5,4±0,14*2	11,3±0,46*1	5,2±0,7*4
IL-17	pg/ml	8,7±0,24	10,6±0,52*1	8,3±0,22*2	22,2±1,03*1,2	15,3±0,71*1,4
IFNγ	pg/ml	15,6±0,27	22,3±0,83*1	22,2±0,85*1	23,3±0,9*1	28,6±0,83*1,4
IL-10	pg/ml	2,7±0,13	3,7±0,22*1	8,4±0,3*1,2	3,9±0,32*1	4,1±0,29*1
IL-1RA	pg/ml	137,7±1,68	149,7±2,55*1	133,9±2,59*2	167,7±2,67*1,2	178,0±3,29*1,4
C_3	mg/dL	82,2±1,79	67,6±3,8*1	83,8±3,92*2	65,1±2,45*1	78,4±3,13*4
C_{3a}	ng/ml	38,2±2,1	46,8±1,4*1	40,3±2,6*2	47,0±1,8*1	39,9±2,7*4
C_4	mg/dL	24,0±0,54	25,1±1,4	23,8±1,42	25,7±1,04	24,8±1,12
C_5	mg/dL	0,101±0,01	0,052±0,02*1	0,091±0,01*1,2	0,049±0,01*1	0,071±0,01*1,4
C_{5a}	ng/ml	78,4±4,5	125,3±7,8*1	91,3±4,9*1,2	131,5±8,1*1	105,6±7,7*1,4
C_1-inh.	ng/ml	288,5±3,65	274,0±4,33*1	278,8±2,2*1	272,2±3,29*1	273,1±2,61*1
Factor H	ng/ml	39,7±1,02	39,4±1,1	40,5±0,95	36,7±2,1	40,7±2,55

Note: in this table and in tables 2,3 an asterisk marks significant differences in arithmetic means (p <0.05); the numbers next to the asterisk - in relation to the indicators of what group these differences are given..

In patients with CCI stage II, upon admission to the clinic the blood plasma was found to be generally similar in the direction to changes in the content of cytokines and indicators of the complement system. The level of IL-17 turned out to be increased by 2,6 times, the concentration of TNFα – by 3,9 times, IL-1β – by 2,1 times, IFNγ - 1.2 times, IL-10 and IL-1RA by 1.4 and 1.2 times respectively. There was also a decrease in the concentration of C_3 and C_5 components of the complement and C_1-inhibitor by 1,3, 2,1 and 1,1 times, respectively, an increase in the content of C_{3a} and C_{5a} by 1,2 and 1,7 times, the level of C_4- component of the complement and factor H remained within normal limits. The performed treatment normalized the concentration of IL-1β, C_3 and C_{3a}, corrected the level of TNFα, IL-17, C_5 and C_{5a}-complement components towards the values of healthy donors, the content of IL-10 and C1-inhibitor did not change, and the concentration of IFNγ and IL-1RA increased even to a greater extent (Table 1). Prior to the treatment in patients with CCI stage I, at the systemic (blood plasma) and local (erythrocytes) levels the activation of peroxidation processes was established (an increase in the concentration of MDA in the blood plasma and erythrocytes by 3,4 and 4,8 times respectively and AHP by 6,2 and 4,7 times), a decrease in antioxidant defense factors (a decrease in blood plasma and erythrocytes of TAA by 1,3 times, SOD activity by 1,5 and 1,3 times respectively and catalase by 1,3 and 2 times). In the blood plasma and erythrocytes there was an increase in the level of SM_{NO} by 2,8 and 2,2 times respectively. In addition, there was an increase in the concentration of the antioxidant neopterin by 1,6 times, CRP by 3,8 times and a decrease in endothelin-1 by 2,3 times at the systemic level. After the treatment performed, the activity of catalase in the blood plasma and erythrocytes returned to the normal value, and the TAA and the content of lipid peroxidation products shifted towards the level of healthy donors. At the systemic level the concentration of SM_{NO} and CRP was corrected but not to normal values, the level of neopterin increased even to a greater extent, the activity of SOD and the content of endothelin-1 did not change. In erythrocytes the level of SM_{NO} normalized and the SOD activity increased above the control values (Tables 2, 3).

Table 2. Metabolic Indicators of the Blood Plasma in Patients with CCI Stages I and II (M ± m)

Indicators	Units of measurement	1	2	3	4	5
			CCI-1		CCI-2	
		Healthy	Prior to the treatment	After the treatment	Prior to the treatment	After the teratment
MDA	mmol/L	0,94±0,04	3,23±0,19*1	1,37±0,09*1,2	3,33±0,13*1	1,86±0,04*1,4
AHP	stand.unit	0,13±0,01	0,8±0,05*1	0,28±0,02*1,2	0,88±0,04*1	0,67±0,03*1,4
TAA	%	44,3±1,11	34,4±0,61*1	39,7±0,62*1,2	37,8±0,75*1,2	41,0±0,54*1,4
SOD	pg/ml	53,8±1,44	36,3±1,61*1	38,6±1,16*1	39,2±0,85*1	44,6±0,96*1,4

Catalase	mcat/L	21,9±0,56	16,9±0,44*1	22,1±0,53*2	18,1±0,35*1,2	22,0±0,43*4
Neopterin	pg/ml	5,1±0,09	8,2±0,24*1	10,5±0,2*1,2	9,2±0,3*1,2	10,3±0,28*1,4
Endothelin-1	fmol/ml	2,31±0,08	0,99±0,04*1	1,03±0,05*1	0,91±0,05*1	1,09±0,08*1
CRP	mg/dL	1,1±0,03	4,21±0,22*1	1,61±0,08*1,2	3,72±0,15*1,2	2,07±0,12*1,4
SM_{NO}	mmol/L	1,2±0,06	3,36±0,24*1	1,62±0,08*1,2	3,54±0,15*1	2,38±0,18*1,4

Table 3. Metabolic Indicators in the Erythrocytes in Patients with CCI Stages I and II (M ± M)

Indicators	Units of measurement	1	2	3	4	5
			ХИМ-1		ХИМ-2	
		healthy	Prior to the treatment	After the treatment	Prior to the treatment	After the treatment
MDA	mmol/L	0,31±0,02	1,49±0,07*1	0,66±0,04*1,2	1,6 8±0,1*1	0,44±0,02*1,4
AHP	stand.unit	0,18±0,01	0,84±0,06*1	0,38±0,01*1,2	0,9±0,03*1	0,42±0,02*1,4
TAA	%	31,1±0,8	23,7±0,84*1	29,6±0,92*1,2	24,8±0,77*1	29,4±0,63*1,4
SOD	stand.unit	19,2±0,72	13,2±0,48*1	23,5±0,62*1,2	13,4±0,52*1	19,3±0,95*4
Catalase	mcat/L	9,57±0,31	4,84±0,18*1	9,48±0,29*2	4,88±0,17*1	9,7±0,36*4
SM_{NO}	mmol/L	2,28±0,14	4,94±0,18*1	2,55±0,19*2	4,78±0,14*1	3,51±0,09*1,4

In patients with CCI stage II upon admission to the clinic, laboratory metabolic changes similar in direction if compared with the stage I were revealed: activation of LPO processes with a decrease in antioxidant defense factors at the systemic and local levels, which was evidenced by an increase in the level of MDA and AHP in the blood plasma and erythrocytes, by 3,5 and 5,4 times respectively, a decrease in TAA by 1,2 and 1,3 times, SOD activity by 1,4 times and catalase by 1,2 and 2 times. In the blood plasma and erythrocytes there was an increase in the level of SM_{NO} by 3,0 and 2,1 times, respectively, in the plasma of the antioxidant neopterin - by 1.8 times, CRP - by 3.4 times and a decrease in endothelin-1 by 2,3 times. The performed treatment normalized at the systemic and local levels the activity of catalase, and the TAA, the concentration of LPO and SM_{NO} products shifted towards the values of healthy donors. In the plasma the level of CRP approached the control values, the content of neopterin increased even to a greater extent, the concentration of endothelin-1 did not change. In the erythrocytes SOD activity returned to the normal values (Tables 2, 3). Thus, among the 28 investigated parameters of the immune and metabolic status in patients with CCI stages I and II upon the time of their admission to the clinic, 26 (92,9%) indicators (excluding the indicators of the complement system: component C_4 and inhibitor factor H) were changed from the values of healthy donors respectively, 73,1% of these indicators turned out to be the same in magnitude and direction of changes, and 26,9% were identical in direction. It can be concluded that profound immunometabolic disorders took place, which were the same on the part of laboratory markers at both stages of the disease, that could be considered as immune inflammation, oxidative stress, endothelial dysfunction, LPO activation, interrelated and interdependent among themselves, which results in the blockage of vessels of various sizes and CCI development, where energy deficiency becomes the main pathobiochemical component of the syndrome of cellular, tissue and organ ischemia. It should be noted that the course of pharmacotherapy, which included antihypertensive, metabolic, nootropic and antioxidant preparations, did not normalize 61,5% of the studied laboratory immunometabolic parameters changed prior to the treatment in patients with CCI stage I and 76,9% of those with stage II. The presence of immune inflammation in the patients studied is confirmed by an increased level of TNFα (the primary mediator of inflammation involved in the pathogenesis of most infectious and immunopathological diseases, coordinating the inflammatory response and cytokine cascade: IL-1β, IL-6, IL-8), IL-1β (the main mediator for the development of a local inflammatory reaction, is included in a complex of protective reactions), IFNγ (a mediator of Th-1 cells activation that activate macrophages expressing the enzymes responsible for the formation of reactive oxygen species, NO synthase, NO formation), IL-17 (induces pro-inflammatory effect through activation of IL-1, IL-6, IL-8, TNFα, G-CSF release by immunocytes and endothelial cells, stimulates the formation of VEGF, angiogenic factors, increases the number of neutrophils), by activation of the complement system (decrease in the initial components of complement C_3 and C_5 with an increase in the level of C_{3a} and C_{5a} fragments - active chemotactic and vasodilator factors - released upon that have anaphylactogenic activity and participate in inflammation and hypersensitivity reactions) with the absence of a compensational inhibitor (factor H) increase or even its decrease (C1-inh.). Besides, the complement system interacts with other humoral systems that are activated during inflammatory processes and promotes the involvement of these systems in the immune inflammation response. Finally, the deposition of complement components in the composition of immune complexes on biological membranes initiates the development of immunopathology that results from the attraction of macrophages and other effectors of immune inflammation to the affected area [10-16]. The development of oxidative stress (imbalance between prooxidants and antioxidants, in which prooxidants prevail) in CCI stages I and II is evidenced in our studies by an increase at the systemic (blood plasma) and local levels (erythrocytes) in the concentration of LPO products (MDA, AHP), SM_{NO} and CRP (a marker of a systemic inflammatory response), by a significant decrease in antioxidant defense indicators (TAA, SOD activity, catalase), a compensational increase in the content of neopterin [17-19]. Excessive production of reactive oxygen intermediate (ROI - superoxide anion radical, peroxide anion, hydroxyl radical, nitric oxide, peroxynitrite) during oxidative stress overcomes the defensive function of the antioxidant mechanisms of the cell and becomes a strong pathogenic factor, damaging mitochondrial membranes, proteins, suppressing the cell key

functions, including aerobic oxidation and oxidative phosphorylation, which results in the further formation of ROI, thereby mediating LPO and DNA damage, that causes changes in the functions of the vascular endothelium, an increase in the synthesis of adhesive molecules, adhesion and penetration of monocytes into the vascular wall, attraction of pro-inflammatory proteins and cells, an increase in platelet aggregation, and thrombi formation [20 – 22]. We found out that at both stages of CCI the concentration of stable end products - nitrite and nitrate (indirect markers of the concentration of nitric oxide in the body), which are the product of nitric oxide with oxygen reaction, is increased in the blood and erythrocytes, and these processes were closely related to the formation and functioning of ROI. In presence of physiological conditions NO is one of the most powerful vasodilators, it takes an active part in the regulation of vascular tone and blood flow, blood pressure, systemic and regional hemodynamics, inhibits the formation of endothelial vasoconstrictor factor endothelin-1 and norepinephrine release, prevents the excessive effects of other vasoconstrictors (angiotensin, thromboxane A). In the context of pathological conditions, inductive agents for inducible (iNOS) nitric oxide synthase are endotoxin, IL-1, INFγ, TNFα, and the combined action of IFNγ and TNFα is considered to be optimal (we also revealed an increased level of these cytokines and IL-1β). High NO concentrations have a direct cytotoxic, immunogenic effect, a sharp vasodilation occurs, vascular permeability increases, edema forms, and there is a subsequent development of an inflammatory reaction. This activates the release of IL-1β, IL-6, IL-8, and other inducers of the inflammatory response, NO combines with superoxide anion, forms peroxynitrite (ONOO-), which causes damage to cell membranes and DNA, mutations, apoptosis, contributing to the further development of inflammatory processes and other disorders [23-27]. The presence of endothelial dysfunction in patients with CCI, which ultimately results in a disruption of the blood-brain barrier and starting of neuroimmune self-aggression, is evidenced by an imbalance between the production of vasodilatory (NO) and vasoconstrictor (endothelin) factors, an increased level of proinflammatory Fα, IL- (TN 1, IL-17) and CRP [12, 15, 19, 28-31].

5. CONCLUSION

The obtained results indicate that in patients with CCI stages I and II in presence of hypertension, similar laboratory immunometabolic disorders were revealed, indicating the presence of immune inflammation, oxidative stress, endothelial dysfunction, and LPO activation. All the above mentioned proves that there is a need for intervention in the pathological process, recovery of the nervous system normal functioning and reduction of disabling consequences. The performed standard treatment does not normalize most of the altered parameters of the immune and metabolic status, which necessitates, in its turn, the search for remedies which are to correct disorders at various stages of CCI by means of complex pharmacotherapy with various combinations of antioxidant, nootropic, metabolic preparations used to treat cerebrovascular pathology, and introduction of immunomodulators into the accepted therapeutic regimens as well. Thus, seeking new means and cures able to correct disorders at various stages of CCI by means of complex pharmacotherapy with different combinations of antioxidant, nootropic, metabolic preparations utilized to treat cerebrovascular pathology can be recommendable for the future studies.

6. AUTHORS CONTRIBUTION

S.A.A. and L.E.S. and B.O.N. and D.V.T. devised the project, the main conceptual ideas and proof outline. S.A.A. and L.E.S. and B.O.N. and D.V.T. designed and performed the experiments. S.A.A. and L.E.S. and B.O.N. and D.V.T. discussed the results and commented on the manuscript. Both authors supervised the study.

7. CONFLICT OF INTEREST

Conflict of interest declared none.

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