

Abstract

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**MODERN TREATMENT METHODS OF THE LOCALIZED
INFLAMMATORY RESPONSE IN ACUTE CEREBRAL
ISCHEMIA**

The article shows the results of a complex study of the leading index changes of the cytokine profile in patients with the brain infarction (BI) in the course of therapy with human cryopreserved cord blood serum (CCBS). Plasma levels of proinflammatory cytokines (interleukine-6 (IL-6), tumor necrosis factor- α (TNF- α)) as well as anti-inflammatory factors – IL-4, IL-10 were tested in the blood serum of 350 patients in the mentioned medical condition on the 1st, 10th and 21st days of therapy.

All patients were divided into 2 groups: the 1st one (n = 175) got undifferentiated therapy with the additional administration of acetylsalicylic acid (ASA); the 2nd one (n = 175) got the therapy of 1st group complemented by administration of 1 ml of CCBS within 10 days. Additionally there were 2 more clinical sub-groups distinguished by National Institutes of Health Stroke Scale (NIHSS) according to disease severity level: A group (n = 183) included patients in medium severity condition; B group (n = 167) comprised patients in critical condition. Plasma levels of IL-4, IL-6, IL-10 and TNF- α were specified by means of enzyme-linked immunosorbent analysis.

Summing up the above-mentioned, it is certain that the imbalance in immune system functioning, represented by a simultaneous lytic level increase of both proinflammatory (IL-6, TNF- α) and anti-inflammatory (IL-4, IL-10) cytokines, is observed shortly after the start of BI.

Additional administration of CCBS in a therapeutic complex caused more considerable and more rapid stabilization of proinflammatory factor values, which were ultimately close to the control ones. This substantially influenced the course of disease and its prognosis. The research showed no accurate reduction in anti-inflammatory cytokines levels of IL-4 and IL-10 which indicated intensive localized inflammatory response even at the end of the acute period of disease. However, comparing the mentioned values with those of the patients who were not additionally treated with CCBS, lower value levels have to be acknowledged. It may be explained by a more efficient and incipient reduction of proinflammatory cytokines concentration in the course of disease, which in its turn results in normalization of IL-4 and IL-10 levels.

Keywords: immune monitoring, cytokine, inflammation, ischemia, interleukine, imbalance.

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Резюме

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СУЧАСНІ МОЖЛИВОСТІ ЛІКУВАННЯ ЛОКАЛЬНОЇ ЗАПАЛЬНОЇ РЕАКЦІЇ ПІД ЧАС ГОСТРОЇ ЦЕРЕБРАЛЬНОЇ ІШЕМІЇ

В статті наведені результати комплексного вивчення особливостей змін провідних показників цитокінового профілю хворих на інфаркт головного мозку (ІГМ) в динаміці лікування кріоконсервованою сироваткою кордової крові (КСКК) людини. Були досліджені плазмові рівні як прозапальних цитокінів (інтерлейкін-6 (ІЛ-6), фактор некрозу пухлин- α (ФНП- α)), так і протизапальних чинників – ІЛ-4, ІЛ-10 в сироватці крові 350 хворих з даною патологією на 1-шу, 10-ту і 21-шу добу лікування.

Всі хворі були розділені на 2 групи: 1-ша (n = 175), що отримувала недиференційовану терапію з додатковим призначенням ацетилсаліцилової кислоти (АСК); 2-га (n = 175) – терапія 1-ої групи, що була доповнена введенням 1 мл КСКК протягом 10 діб. За допомогою National Institutes of Health Stroke Scale (NIHSS) також було виділено 2 клінічні підгрупи за ступенем тяжкості: А (n = 183) – хворі в стані середнього ступеня тяжкості; В (n = 167) – хворі в тяжкому стані. Визначення плазмових рівнів ІЛ-4, ІЛ-6, ІЛ-10, ФНП- α проводили методом твердофазного імуноферментного аналізу.

В результаті було отримано дані про те, що вже з перших годин ІГМ спостерігається дисбаланс у функціонуванні імунної системи, який проявляється в одночасному літичному підвищенні рівнів як прозапальних (ІЛ-6, ФНП- α), так і протизапальних (ІЛ-4, ІЛ-10) цитокінів.

Додаткове застосування у лікувальному комплексі КСКК викликало більш значну та швидко стабілізацію значень прозапальних чинників, які були максимально наближені до контрольних, що суттєво впливало на перебіг і прогноз захворювання. Достовірного зниження рівнів протизапальних цитокінів ІЛ-4 та ІЛ-10 у ході дослідження виявити не вдалося, що говорить про вираженість локальної запальної реакції навіть на кінець гострого періоду захворювання. Але порівнюючи значення їх із групою хворих, що додатково не отримували КСКК, доводиться констатувати все ж таки більш низькі рівні даних показників. Можливо це пояснюється більш чітким і раннім зниженням концентрацій прозапальних цитокінів у динаміці захворювання, що в свою чергу призводить до нормалізації рівнів ІЛ-4 і ІЛ-10.

Ключові слова: імунологічний моніторинг, цитокін, запалення, ішемія, інтерлейкін, дисбаланс.

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Introduction

The localized inflammatory response of the brain tissue within acute anoxia occurs due to rapid formation of cytokines, which are specific bioregulatory glycoproteins. By their functional properties they are divided into pro- and anti-

inflammatory units [1, 2].

Interleukine-6 (IL) is one of the main triggers of the cytokine system in acute brain infarction (BI), which acts as a potent promotor of the hypothalamo-pituitary-adrenal axis via the transmembrane receptors gp130 [3], and is synthesized not only by the cells of the immune

system (monocytes, macrophages, lymphocytes, microglial cells), but also by endotheliocytes, astrocytes and unstriated myocytes of blood vessels [4, 5].

Except being a mediator of inflammatory processes, tumor necrosis factor- α (TNF- α) is also a key molecule in regulation of normal differentiation, development and metabolism of different tissues [6, 7]. Due to its binding to the targeting membrane receptors at molecular level the signaling events are started that result in activating the transcription factors which in their turn control the activity of genes which encode the fusion of proinflammatory cytokines and cause a programmed cell death [8, 9].

TNF- α promotes the universal transcription factor NF- κ B, a group of multifunctional intracellular signaling pathways involving mitogen-activated protein kinases which control gene expression of immune response, apoptosis, proliferation, cell cycle control and angiogenesis [10, 11].

In the course of BI the presence of cerebral endothelium is frequently distinguished. That is TNF- α which makes special importance in its progression. TNF- α is proved to promote endothelium permeability, increase procoagulative capacity and reduce anticoagulative features along with accumulation of immune cells in tissues. TNF- α can also start the signaling events which result in activating the endotheliocytes apoptosis in vitro [6, 12].

In the course of acute cerebral ischemia an extensive induction of TNF- α is caused by the oxidative stress and glutamate excitotoxicity after the very first hour of neurologic disorder onset [13].

In the human's body there also exists an antagonist of the proinflammatory cytokine system which deactivates acute stress reactions. These effects can be realized due to the hyperproduction of anti-inflammatory triggers [14], one of which is IL-4. It is involved in T-helpers differentiation, controls the production of TNF- α , IL-1 β , IL-6 and IL-8, activates the macrophages, and strengthens their cytotoxic capabilities. In the course of acute hypoxia of brain tissue the maximum value of IL-4 gene expression is reached in first 6 hours, while the factor synthesis peaks in 48 hours. The highest production of IL-4 in vitro is observed on the 3rd day [15].

The mentioned cytokine promotes expression of the products of class II major histocompatibility system as well as antigen-presenting cells. To some extent it can be regarded as a functional analogue of interferon- γ [16, 17]. IL-4 causes an anti-

inflammatory effect by deactivating the functions of macrophages and their secretion of IL-1, IL-6, IL-8 and TNF- α [18].

Another important anti-inflammatory cytokine is IL-10, which is primarily produced by such immune cells as T-helpers, B-lymphocytes, monocytes and macrophages. An acute cerebral hypoxia causes the hyperproduction of IL-10 by these cells [19].

It acts as an inflammation inhibitor due to synthesis depression of other cytokines, chemokines and adhesive molecules, primarily of TNF- α , IL-1, IL-6, IL-12 and others. This cytokine can depress the effector functions of macrophages, T-killers, neutrophils, synthesis of interferon- γ , the process of expression of adhesion molecules and alternatively stimulate chemotaxis, poliferation and thymocytes maturation [20, 21].

Being a protective factor for vascular endothelium, IL-10 greatly decreases the action of angiotonin II in the course of BI, which is always activated by the outputs of oxidative stress. It can modulate the reconstruction of vessels, reduce adhesion of leucocytes, improve leucocytal and endothelial interaction and provide vasodilatation by increased production of NO [22, 23].

Various immunoinflammatory reflexes are observed almost in all kinds of acute cerebrovascular pathology, while BI is the classic case of amicrobic inflammatory process which starts along with forming the necrotic zone of brain tissue and directly influences the damage severity. The intensity of system reactions in the course of inflammation is mainly determined by the levels of proinflammatory cytokines, prostaglandins, kinin and some hormones with leading values of IL-6 and TNF- α [24]. The initial rapid increase of their content in blood is the appropriate response of the immune system to the caused damage and has to promote the recruitment of immunodefence. Therefore, the immune monitoring in BI follow-up is prior in this case. It makes possible to estimate the level of damage and to make prognosis of the further course and outcome of disease [1, 25].

The objective was to perform a complex study of the character of changes of cytokine profile based on the patients' medical condition in acute brain infarction in the course of therapy with CCBS in order to estimate its immune modulating properties.

Methods and materials. The levels of proinflammatory (IL-6 and TNF- α) and anti-inflammatory (IL-4 and IL-10) cytokines were studied in the blood serum of 350 patients in

mentioned medical condition during their hospitalization on the 1st, 10th and 21st days of therapy in order to determine the degree of changes of cytokine profile in the course of BI.

The patients with BI were treated with a solution of human cryopreserved cord blood serum (CCBS) "Cryocell-cryocord", which contained a set of different hemopoietins, growth factors, adaptogens and reproductive immune response-modulating agents. The solution was developed and produced by SI of ISC of Cryobiology and Cryomedicine of the National Academy of Sciences of Ukraine, Academy of Medical Sciences and Ministry of Health Care of Ukraine (Kharkiv, Ukraine).

According to the medicamentous therapy all patients were randomly divided into 2 groups before the start of treatment: the 1st one (n = 175) got undifferentiated treatment with the additional administration of ASA; the 2nd one (n = 175) got undifferentiated therapy with the additional administration of ASA complemented by administration of 1 ml of CCBS solution intravenously within 10 days. Both groups of patients had the same clinical features of disease, comorbidity, age and sex.

The patients were graded by National Institutes of Health Stroke Scale (NIHSS) according to their disease condition and the degree of neurologic deficit by 15 indexes, which were stated in points rated at the first hours of disease and in the course of therapy on the 10th and 21st day. Thus, all patients were divided into 2 clinical sub-groups: A group (n = 183) included patients in medium severity condition (an average point scaled by NIHSS in the 1st group was 11.74 ± 0.33 and 11.61 ± 0.22 in the 2nd one); B group (n = 167) comprised patients in critical condition (an average point scaled by NIHSS in the 1st group was 23.11 ± 0.37 and 24.06 ± 0.29 in the 2nd one).

Plasma levels of IL-4, IL-6, IL-10 and TNF- α were specified by enzyme-linked immunosorbent analysis. The statistical results were processed by Statistica 6.0 program.

Results. The analysis showed that average values of IL-6 proved to be the highest in blood serum of the patients with BI at the moment of hospitalization. At the same time these values exceeded the indexes of the control group almost ten-fold (34.33 ± 2.9 pg/ml in patients with severe BI compared to 3.51 ± 0.28 pg/ml in the control group, $p < 0.001$). Patients with medium severity condition of BI had 5 times higher IL-6 indexes (17.62 ± 2.3 pg/ml, $p <$

0.001) than the control group. The detected changes can indicate a considerable and early stress of the cytokine system in all patients, which is maximal in severe BI.

All severity-specific sub-groups of both groups had a firm reduction of plasma levels of IL-6 after the therapy compared to the indexes at the moment of hospitalization ($p < 0.05$). In A sub-groups of both groups the levels of IL-6 were close to each other on the 10th day of disease. There was a certain reduction of indexes compared to those of the 1st day after the acute neurological symptoms onset by 15.5 % and 37.3 %, respectively. It is attributable to the fact that in the not-critical brain tissue injury the levels of proinflammatory cytokines can approach to the stated values within a shorter period of time than in severe conditions. Apparently it takes place due to the early activation of anti-inflammatory factors.

On the 10th day reliably lower values of IL-6 were detected in patients with severe BI of the 2nd group in comparing to the corresponding indexes of the patients not treated with CCBS ($p < 0.05$) additionally. As for the percentage correlation the levels of IL-6 in patients with severe BI of the 2nd group reliably reduced by 48.5% on the 10th day of disease whereas the 1st group showed the reduction only by 30.1 %. Still a considerable difference in 18.4% can be indicative of the anti-inflammatory effects of CCBS being presented even in considerable injuries.

On the 21st day of therapy the levels of IL-6 were close to the control values almost in all groups of patients. It was clearly observed in patients of the 2nd group of A sub-group additionally treated with CCBS.

Seriously ill patients of both groups showed the highest TNF- α values (20.15 ± 0.71 and 21.06 ± 0.50 pg/ml correspondingly). This fact indicated the maximal strain of the cytokine system in the course of severe BI. Patients in severe condition of all sub-groups and patients in medium severity condition in the 1st group had tendency to reduction of TNF- α values on the 10th day of BI comparing to initial indexes registered on the 1st day, but it was not statistically significant. While analyzing the indexes of the 2nd group, the reduction of TNF- α levels was also noticed in patients of both severity-specific sub-groups on the 10th day of disease, which was statistically significant only in the severe condition group of patients ($p < 0.05$).

A certain reduction of TNF- α level was also observed in patients of the 2nd sub-group on the 21st

day of therapy, but its average value (7.24 ± 0.22 pg/ml) was a bit higher than that of A sub-group (5.34 ± 0.15 pg/ml). The patients of the 2nd group with severe BI additionally treated with CCBS had a considerably lower level of TNF- α than the patients of the 1st group ($p < 0.05$): 7.24 ± 0.22 pg/ml and 12.63 ± 0.47 pg/ml, correspondingly.

The study showed that patients with severe BI had the highest level of anti-inflammatory cytokin IL-4 in blood serum at the moment of hospitalization. Besides, its level was almost 3,6 times higher than the indexes in the control group (5.28 ± 0.34 pg/ml in both sub-groups compared to 1.48 ± 0.21 pg/ml of the control group, $p < 0.001$). Patients in medium severity condition of BI also had higher IL-4 indexes than those of the control group, but only by 2.5 times (3.74 ± 0.69 pg/ml, $p < 0.05$). The detected changes can be indicative of a functional strain of the anti-inflammatory system in all patients with BI which is fully observed in the course of severe conditions.

On the 10th day of therapy lower values of IL-4 were detected in patients with severe BI of the 2nd group in comparing to the corresponding indexes of the 1st group ($p < 0.05$). As for the percentage correlation, the levels of IL-4 in patients with severe BI of the 2nd group reliably reduced by 28.3% on the 10th day of disease whereas the 1st group showed the reduction only by 17.9 %.

On the 21st day of the therapy the changes in levels of the mentioned index proved to be positive, since the values were close to the control ones almost in all groups of patients. It was firmly stated in patients of the 2nd group of A sub-group additionally treated with CCBS. Patients with severe BI had the highest level values of IL-4 (3.25 ± 0.29 pg/ml) on the 21st day of a standard medical therapy, which still exceeded the control indexes by 2.2 times.

Besides, the patients with acute BI had the highest level of IL-10 in blood plasma on the 1st day of the therapy, while it exceeded the indexes of the control group almost by 4,4 times (2.52 ± 0.44 pg/ml in both sub-groups compared to 0.57 ± 0.17 pg/ml of the control group, $p < 0.001$). Patients in medium severity condition of BI had 3.5 times higher IL-10 indexes (2.00 ± 0.16 pg/ml, $p < 0.05$) than the patients in the control group.

Conclusions

Summing up the above-mentioned, it is certain that the imbalance in immune system functioning, represented by a simultaneous lytic level increase

In the course of the therapy all severity-specific sub-groups of both groups had reduction of IL-6 levels in blood plasma compared to the indexes of the first day. On the 10th day of the therapy, the patients in medium severity condition of BI had a slight reduction of index values compared to those stated at the moment of hospitalization, still it was not statistically significant. Similar findings proved to be in both groups of patients with severe condition ($p > 0.05$).

On the 21st day of the therapy the changes in levels of IL-10 in blood serum gradually reduced almost in all groups of patients, but the values didn't even get close to those of the control group. A certain reduction of IL-10 levels was stated only when comparing the values studied at the moment of hospitalization and on the 21st day of disease in both sub-groups of the group of patients which were additionally treated with CCBS in 3,6 and 2 times, correspondingly.

The direct correlation relationship between an average clinical result scaled by NIHSS and values of IL-6 ($r = + 0.89$; $p < 0.05$), TNF- α ($r = + 0.89$; $p < 0.05$) IL-4 ($r = + 0.95$; $p < 0.05$) and IL-10 ($r = + 0.97$; $p < 0.05$) was fixed in the course of statistical analysis. This correlation persisted throughout the therapy and was indicative of dependence of cytokine levels in blood plasma and a patient state in disease onset.

The direct correlation relationship between the levels of IL-6 and IL-4 ($r = +0.87$; $p < 0.05$), TNF- α and IL-4 ($r = +0.86$; $p < 0.05$), IL-6 and IL-10 ($r = + 0.91$; $p < 0.05$) as well as TNF- α and IL-10 ($r = + 0.88$; $p < 0.05$) is indicative of the potent simultaneous activation of pro- and anti-inflammatory cytokin systems in the course of BI.

Discussion. The measured changes of the cytokin system enable us to regard them as a special incipient and adaptable body mechanism in acute BI. The disease severity level is one of the key factors, which can substantially influence the degree of changes of leading pro- and anti-inflammatory factors. The results of the experiment suggest that CCBS has a powerful immunomodulating effect due to involving the interferons and anti-inflammatory cytokins (IL-4, IL-8 and IL-10).

of both proinflammatory (IL-6, TNF- α) and anti-inflammatory (IL -4, IL -10) cytokines, is observed shortly after the start of BI.

The detected characteristics confirm the direct

relation of the indicated factors to the early onset of both activation and suppression of the localized starting reaction because of the ischemic injury of brain tissue and their further functioning in the pathogenetic mechanisms of the acute cerebral ischemia progression.

Additional administration of CCBS in a therapeutic complex caused more considerable and more rapid stabilization of IL-6 and TNF- α values, which were ultimately close to the control ones. This substantially influenced the course of disease and its prognosis. The research showed no accurate

reduction in anti-inflammatory cytokines levels of IL-4 and IL-10, which indicated intensive localized inflammatory response even at the end of the acute period of disease. However, comparing the mentioned values with those of the patients who were not additionally treated with CCBS, lower value levels have to be acknowledged. It may be explained by a more efficient and incipient reduction of proinflammatory cytokines concentration in the course of disease, which in its turn results in normalization of IL-4 and IL-10 levels.

Conflict of interest

The authors declare no conflict of interest.

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