Медицинская иммунология
2021, Т. 23, № 4,
стр. 737-742

Краткие сообщения
Short communications

Medical Immunology (Russia)/
Meditsinskaya Immunologiya
2021, Vol. 23, № 4, pp. 737-742

КОРРЕЛЯЦИОННЫЙ АНАЛИЗ МЕЖДУ ЛАБОРАТОРНЫМИ ИММУННЫМИ И МЕТАБОЛИЧЕСКИМИ ПАРАМЕТРАМИ ПРИ ХРОНИЧЕСКОЙ ИШЕМИИ МОЗГА I И II СТАДИИ НА ФОНЕ ГИПЕРТОНИЧЕСКОЙ БОЛЕЗНИ ПОСЛЕ ЛЕЧЕНИЯ

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Резюме. Проведено определение взаимосвязей между нарушениями лабораторных показателей иммунного и метаболического статуса у пациентов с хронической ишемией головного мозга I-II стадии. В исследование было включено 104 пациента, из которых 76 больных женского пола и 28 мужского, с ХИМ на фоне гипертонической болезни II степени, из которых 52 больных были с I стадией и 52 со II стадией в возрасте 50±5 лет. Кроме того, изучены клинические и лабораторные показатели у 22 здоровых доноров того же возраста. Оценку клинико-лабораторных данных осуществляли в начале лечения и через 2 недели после его окончания. Определяли в плазме крови и эритроцитах сорбционную способность эритроцитов и сорбционную емкость гликокаликса (СЕГ), активность процессов перекисного окисления липидов, состояние антиоксидантной системы, выявляли уровень стабильных метаболитов оксида азота (SMNO), неоптерина, С-реактивного белка, цитокинов (TNFα, IL-1β, IL-8, IFNγ, IL-18, G-CSF, IL-4, IL-10), иммуноглобулинов (IgM, IgG, IgA), компонентов системы комплемента (C3, C4, C5, C5A), фагоцитарную и кислородзависимую активность полиморфноядерных лейкоцитов крови. Проводя сравнительную оценку результатов корреляционного, факторного и кластерного анализов оценки показателей иммунного и метаболического статуса у пациентов с ХИМ I стадии выявлены наиболее значимые лабораторные параметры, необходимые для определения в клинике с целью объективной оценки выраженности иммунных и метаболических нарушений: TNFα, IL-8, IL-10, SMNO и СЕГ. У больных ХИМ II стадии с целью объективной оценки выраженности иммунных и метаболических нарушений рекомендованы TNFα, IL-8, IL-17, IL-10, фагоцитарное число нейтрофилов и СЕГ.

Ключевые слова: хроническая ишемия мозга, взаимосвязи параметров иммунометаболического статуса

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Образец цитирования:

Н.А. Быстрова, А.А. Шульгинова, А.И. Конопля «Корреляционный анализ между лабораторными иммунными и метаболическими параметрами при хронической ишемии мозга I и II стадии на фоне гипертонической болезни после лечения» // Медицинская иммунология, 2021. Т. 23, № 4. С. 737-742. doi: 10.15789/1563-0625-CAB-1992

For citation:

N.A. Bystrova, A.A. Shulginova, A.I. Konoplya "Correlation analysis between laboratory immune and metabolic parameters in chronic brain ischemia stages I and II on the background of hypertension after treatment", Medical Immunology (Russia)/ Meditsinskaya Immunologiya, 2021, Vol. 23, no. 4, pp. 737-742. doi: 10.15789/1563-0625-CAB-1992

DOI: 10.15789/1563-0625-CAB-1992

CORRELATION ANALYSIS BETWEEN LABORATORY IMMUNE AND METABOLIC PARAMETERS IN CHRONIC BRAIN ISCHEMIA STAGES I AND II ALONG WITH HYPERTENSION AFTER TREATMENT

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Abstract. Determination of interrelationships between impairments of laboratory parameters of immune and metabolic status in patients with chronic cerebral ischemia of I-II stages was carried out. The study included 104 patients, of which 76 were female and 28 males, with CCI on the background of II degree hypertension, of which 52 patients were with stage I and 52 with stage II at the age of 50 ± 5 years. Also, clinical and laboratory parameters were studied in 22 healthy donors of the same age. Evaluation of clinical and laboratory data was carried out at the beginning of treatment and 2 weeks after its end. The sorption capacity of erythrocytes and the sorption capacity of the glycocalyx (SEG), the activity of lipid peroxidation processes, the state of the antioxidant system were determined in blood plasma and erythrocytes, the level of stable metabolites of nitric oxide (SMNO), neopterin, C-reactive protein, cytokines (TNFα, IL- 1β, IL-8, IFNγ, IL-18, G-CSF, IL-4, IL-10), immunoglobulins (IgM, IgG, IgA), complement system components (C3, C4, C5, C5A), the phagocytic and oxygen-dependent activity of polymorphonuclear blood leukocytes. Comparative assessment of the results of correlation, factorial and cluster analyzes for assessing the parameters of the immune and metabolic status in patients with stage I CCI revealed the most significant laboratory parameters necessary for determination in the clinic for objective assessment of the severity of immune and metabolic disorders: TNFα, IL-8, IL-10, SMNO and NEG. In patients with CCI stage II, to objectively assess the severity of immune and metabolic disorders, TNFα, IL-8, IL-17, IL-10, the phagocytic number of neutrophils and SEG are recommended.

Keywords: chronic cerebral ischemia, interrelationships of parameters of immunometabolic status

Introduction

In the world and in Russia, cerebrovascular disease (CEH), ranked second in the structure of mortality from circulatory diseases and total mortality, and the prevalence of chronic cerebral ischemia (CHEM) is 60-75% of all CEH. Now up to 10-15% of the population is over 65 years old, it is predicted that in 20 years this figure will approach 20-25% and the number of people over 80 years old will grow most rapidly, and their number may increase 3 times in the next decade. Since 2000, there has been a steady trend towards "rejuvenation" of the population of patients with various types of CVD, which is associated with a steady increase in the impact of adverse external factors and insufficient effectiveness of prevention programs for socially significant diseases, primarily for atherosclerosis and arterial hypertension [1, 3, 4].

Materials and methods

The relationship between violations of laboratory indicators of immune and metabolic status in patients with stage I-II chronic brain ischemia during treatment was determined.

The study included 104 patients, 76 female and 28 male patients, who formed the main group of hospitalized in the neurological Department of the Kursk regional clinical hospital, with correcting level of blood pressure, with CHEM against the background of grade II hypertension, of which 52 patients were stage I and 52 with stage II at the age of 50±5 years.

All patients during their stay in the hospital for 14 days received daily basic pharmacological therapy: an angiotensin-converting enzyme inhibitor – enalapril maleate (Berlipril) (supportive hypotensive therapy) and a vasoactive drug – Vinpocetin (Cavinton).

All patients with CHEM stage I and II were equally divided into 4 groups: within 14 days, all patients of the first groups received Ceretone and Actovegin, 2-4 groups – Cerakson and Mexicor. Patients of the third and fourth groups additionally received immunomodulatory drugs, respectively, Glutoxim and Polyoxidonium.

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The criteria for inclusion in the main group were: age from 40 to 60 years; absence of concomitant diseases in the acute stage, presence of CHEM against the background of grade II, stage II hypertension, risk 2, diagnosed 5 or more years ago in accordance with the recommendations of the world health organization and the International society for arterial hypertension (MOG, 1999).

The exclusion criteria were: symptomatic arterial hypertension; severe or moderate atherosclerotic changes in the fundus vessels; heart rhythm and conduction disorders; chronic heart failure of more than II FC in accordance with the classification of the new York heart Association (NYHA); hemodynamically significant stenoses of brachiocephalic and cerebral vessels, heart defects; myocardial infarction, postinfarction cardiosclerosis and progressive angina or indications thereof a history of diabetes or impaired glucose tolerance.

All patients underwent a comprehensive clinical and instrumental examination according to generally accepted standards, and in all cases, the diagnosis of stage I and II CHEM was verified. The treatment followed the principles of evidence-based medicine.

Evaluation of clinical and laboratory data in groups with CHEM was performed at the beginning of treatment and 2 weeks after its end. From 10 ml of heparinized blood, plasma and red blood cell mass were obtained by centrifugation, with which the sorption capacity of red blood cells (SSE) and the sorption capacity of glycocalyx (SEG) were immediately determined.

The intensity of lipid peroxidation processes was assessed by the content of acyl hydroperoxides and malondialdehyde (MDA and AGP) in blood plasma and erythrocytes.

The state of the antioxidant system was determined by direct/competitive solid-phase enzyme immunoassay using ready-made commercial kits: the activity of superoxide dismutase (SOD) "Bender Medsystems" (Austria) and catalase "Cayman Chemical" (USA). Total antioxidant activity (OAA) was detected by a method based on the degree of inhibition of ascorbate – and ferroinduced oxidation of twin-80 to MDA. The level of stable metabolites of nitric oxide (SMNO) was detected using a set for solid-phase enzyme immunoassay by R&D (England).

In addition, plasma levels of neopterin "IBL" (Germany), endothelin-1 "Biomedica" (Slovakia) and erythropoietin "Biomerica" (USA) were detected by enzyme immunoassay. Ceruloplasmin (CP) was determined by immunoturbidimetry using the sentinel kit (Spain), and C-reactive protein (CRP) using the Vector-best kit (Russia) using the BTS-350 semiautomatic analyzer (BioSystems, Spain).

Cytokines (TNFα, IL-1β, IL-6, IL-8, IFNγ, IL-2, IL-17, IL-18, G-CSF, IL-4, IL-10, IL-1ra) were detected by solid-phase enzyme immunoassay using sets of Vector – best CJSC (Russia), components of the complement system (C3, C3A, C4, C5, C5A) and factor H-diagnostic set of Cytokine LLC (Russia). The activity of the C1-inhibitor was determined by chromogenic method based on the ability to inhibit C1-esterase. Registration of all the results of enzyme immunoassay was performed using a microplate photometer "Sunrise", Tecan (Austria).

The phagocytic activity of polymorphonuclear blood leukocytes after their isolation from the blood on the phycoll-urographin density gradient (d = 1,077) was evaluated by determining the phagocytic index, phagocytic number, and phagocytosis activity index. The activity of oxygen-dependent neutrophil systems was evaluated using a PD 303 SApel spectrophotometer (Japan) based on the nitrosine tetrazolium reduction reaction (nst-test), spontaneous and stimulated by zymosan, the stimulation index and the functional reserve of neutrophils.

In statistical processing of the research results, the χ^2 (Chi-square) criterion was used to compare the qualitative parameters. The Shapiro–Wilk test was used to assess whether quantitative traits belong to a distribution type. The student's t-test was used to compare normally distributed values. The statistical significance of differences in quantitative values with an abnormal distribution was assessed using the Mann–Whitney U-test and the Wilcoxon test (when comparing dependent groups). The values of normally distributed quantitative parameters are represented by the arithmetic mean (M) with the error of the arithmetic mean (m), and abnormally distributed ones are represented by the median (Me) with an interquartile interval ($Q_{0.25}$-$Q_{0.75}$). Relationships were established based on factor analysis, cluster analysis, and Spearman's rank correlation coefficient.

TABLE 1. COMPARATIVE EVALUATION OF CORRELATION AND FACTOR ANALYSIS AND CLUSTER ANALYSIS OF THE ASSESSMENT OF INDICATORS OF THE IMMUNE SYSTEM AND METABOLIC STATUS IN STAGE I CHEM

Indicators	Correlation analysis	Factoral analysis	Clustal analysis
TNFα	+	+	+
IL-1β	+	+	
IL-6	+	+	+
IL-8	+	+	+
IL-17			
IL-18			
IL-4			
IL-10	+++	+	+
IL-1ra	++		
IFNγ			
IL-2	+++		
G-CSF			
C3	++		
C3a			+
C4			+
C5	+++		
C5A			
C_1-inchib.	++		+
Factor N	++++		+
FP			
FCH			
NBT-sp	+++		+
NBT-st.	+		
MDA		+	
AGP		+	
OAA			
SOD			
Catalase			
Cerulo-plasmin			
Neopterin			
Endothe-lin-1		+	
SRB		+	
SMNO	+	+	+
Erythro-poietin	+	+	
*MDA		+	
*AGP		+	
*OAA			
*SOD		+	
*Catalase		+	
*SMNO		+	+
SEG	+	+	+
SSJ		+	+

TABLE 2. COMPARATIVE EVALUATION OF CORRELATION AND FACTOR ANALYSIS AND CLUSTER ANALYSIS OF THE ASSESSMENT OF INDICATORS OF THE IMMUNE SYSTEM AND OXIDANT STATUS IN STAGE II CHEM

Indicators	Correlation analysis	Factoral analysis	Clustal analysis
TNFα	+	+	+
IL-1β		+	
IL-6		+	
IL-8	+	+	+
IL-17	++	+	+
IL-18		+	
IL-4	+		
IL-10	+++	+	+
IL-1ra			
IFNγ	+++		
IL-2	+		
G-CSF			
C3	++		
C3a			+
C4			
C5			
C5A	+		
C_1-ing.			
Factor H	++		+
FP			
FCH	+++	+	+
NBT-sp.	++		
NBT-st.			+
MDA		+	
AGP		+	
OAA			
SOD		+	
Catalase			
Cerulo-plasmin			
Neopterin			
Endothe-lin-1		+	
SRB		+	
SMNO			
Erythro-poietin		+	
*MDA		+	
*AGP		+	
*OAA			
*SOD		+	
*Catalase		+	
*SMNO	+		
SEG	+	+	+
SSJ		+	

Differences were considered statistically significant at $p < 0.05$.

Results and discussion

To identify independent factors in the maintenance of immune and metabolic homeostasis in the studied groups of patients with CHEM, we conducted a factor analysis.

In stage I and II CHEM, the presence of approximately the same factors in importance in each of the groups of patients takes place.

In patients with stage I, the most significant are at the systemic level – TNFα, IL-1β, IL-6, IL-8, IL-10, MDA, AGP, endothelin-1, CRP, SMNO, erythropoietin, and within red blood cells-MDA, AGP, SOD, catalase, SMNO, SEG, and CSE.

In patients with stage II of the disease, according to factor analysis, the most significant indicators are the following in the blood – TNFα, IL-1β, IL-6, IL-8, IL-17, IL-18, IL-10, FH, AGP, SOD, endothelin-1, CRP, erythropoietin, inside red blood cells – MDA, AGP, SOD, SEG and CSE.

A certain proof of integrative processes between laboratory status terms is the presence of reliable correlations between them [2, 5, 6]. After the correlation analysis between the components of the immune and metabolic status in patients with stage I and II CHEM, we analyzed the types of connections: intra-system and intersystem.

The control group documented the presence of 73 reliable correlations, 32 of which are intrasystem, and 41 – between-system. In patients with CHEM I, there are 53 such connections (23 and 30, respectively). In the group of patients CHEM stage I receiving Cereton and Actovegin, such relations 54 (22 and 32 respectively), patients after application Ceraxon and Mexicor such ties 59 (25 and 34 respectively), in patients treated with Ceraxon, Mexico and Glutoxim – 70 (28 and 42 respectively) and in patients who were administered Ceraxon, Mexicor and Polyoxidonium, the maximum observed number of such relationships – 76 (31 and 45 respectively).

The use of cluster analysis revealed the grouping of a number of indicators of the immune status and metabolic link in patients with stage I and II CHEM. Thus, patients of the first and second groups have 4 grouped clusters of indicators, while there are some significant differences in the presented indicators within each of the clusters in groups with CHEM I and CHEM II.

The constructed dendrograms clearly indicate a pronounced maladaptation of the mechanisms for maintaining immune and metabolic homeostasis in the early and later stages of the disease.

By conducting a comparative assessment of the results of correlation, factor and cluster analyses of the assessment of immune and metabolic status indicators in patients with stage I CHEM, it is possible to identify the most significant indicators of immunometabolic status necessary for determining the clinical severity of immune and metabolic disorders: TNFα, IL-8, IL-10, SMNO and SEG (Table 1).

In patients with stage II CHEM, the following parameters can be recommended for determination in the clinic in order to objectively assess the severity of immune and metabolic disorders: TNFα, IL-8, IL-17, IL-10, FH and SEG (Table 2).

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Поступила 02.04.2020
Принята к печати 19.04.2020

Received 02.04.2020
Accepted 19.04.2020