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УРОВЕНЬ ХЕМОКИНОВ И ДРУГИХ МЕДИАТОРОВ ВОСПАЛЕНИЯ У ПАЦИЕНТОВ С МЯГКИМ КОГНИТИВНЫМ СНИЖЕНИЕМ, ПРОХОДЯЩИХ РЕАБИЛИТАЦИЮ

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Резюме. Болезнь Альцгеймера – наиболее распространенное нейродегенеративное заболевание в пожилом возрасте. В части случаев ее развитию предшествует додементная стадия – мягкое когнитивное снижение. Важным компонентом патогенеза нейродегенерации является хроническое нейровоспаление (воспалительная активация микроглии и астроцитов в мозге), развитию и поддержанию которого может способствовать системный воспалительный ответ вследствие нарушения иммунной регуляции. Изучение уровня хемокинов у пациентов с MCI и его взаимосвязи с клиническими проявлениями – актуальное направление исследований, так как показано участие ряда из них в патогенезе нейродегенерации. Целью данного исследования было изучение уровня хемокинов и других медиаторов воспаления в динамике у пациентов с мягким когнитивным снижением на фоне реабилитации, а также исследование его связи с выраженностью когнитивных нарушений. В основную группу исследования вошли 48 пациентов, проходящих курс реабилитации в Клинике памяти Психиатрической клинической больницы № 1. Продолжительность курса составляла 6 недель, программа включала когнитивные тренировки, психотерапию и самостоятельное выполнение заданий. Пациенты прошли иммунологические исследования и клиническую оценку в динамике. Повторное обследование проводилось через 6 месяцев после начальной точки. В контрольную группу вошли 46 здоровых добровольцев, сопоставимые с пациентами по возрасту и полу. Для определения концентрации цитокинов и хемокинов в сыворотке крови использовали мультиплексный анализ. Для оценки достоверности различий использовали критерий Стьюдента. Оценка когнитивных функций проводилась с исполь-

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зованием международных нейропсихологических шкал, включая Монреальскую когнитивную шкалу и Краткую шкалу оценки психического статуса. Обнаружено повышение у пациентов уровня ряда цитокинов и хемокинов (TNFα, CXCL10/IP10, CCL22/MDC), регулирующих системное воспаление, клеточные и гуморальные механизмы адаптивного иммунитета. Выявлена взаимосвязь уровня хемокина CCL7 с параметрами нейропсихологического обследования пациентов: обнаружено, что снижение его содержания ассоциировано с более высокой тяжестью когнитивных расстройств. На фоне проведенной реабилитации отмечалось увеличение числа баллов по шкале MMSE, снижение уровня провоспалительного цитокина TNFα, а также хемокинов CXCL10, CCL22 более чем у 50% пациентов. Полученные данные вносят вклад в понимание роли хемокинов в патогенезе мягкого когнитивного снижения и указывают, что их уровень может являться потенциальным биомаркером тяжести когнитивных нарушений. Для последующей трансляции полученных данных в клиническую практику необходима их валидация в более крупных исследованиях, а также оценка взаимосвязи уровней хемокинов с выраженностью когнитивных нарушений при MCI в динамике долгосрочного наблюдения.

Ключевые слова: болезнь Альцгеймера, воспаление, Монреальская когнитивная шкала, мягкое когнитивное снижение, реабилитация, хемокины

LEVELS OF CHEMOKINES AND OTHER INFLAMMATORY MEDIATORS IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT UNDERGOING REHABILITATION

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Abstract. Alzheimer's disease is the most common neurodegenerative disease in old age. In some cases, it is preceded by mild cognitive impairment (MCI). One of the important components in the pathogenesis of neurodegeneration is chronic neuroinflammation (inflammatory activation of microglia and astrocytes in the brain). Systemic inflammatory response and immune dysregulation may contribute to neuroinflammation. The purpose of this study was to investigate the level of chemokines and other inflammatory mediators in patients with MCI who underwent medical rehabilitation, and to study its associations with the severity of cognitive impairment. The study group included 48 patients with MCI undergoing rehabilitation. Rehabilitation included cognitive therapy, psychotherapy and tasks for unaided performance. Repeated examination was conducted 6 months after the completion of rehabilitation. The control group included 46 healthy volunteers. Multiplex assay was used to determine serum cytokine and chemokine concentrations. Student's t-test was used to assess the significance of differences. Assessment of cognitive functions was performed using international neuropsychological scales. In patients with MCI, we have found an increase in the levels of several cytokines and chemokines (TNFα, CXCL10/IP10, MDC) that regulate systemic inflammation, cellular and humoral mechanisms of adaptive immunity. After the rehabilitation course their levels returned to normal. It was also found that decrease in CCL7 level in the patients before the rehabilitation course is associated with the severity of cognitive impairment. The findings contribute to understanding the role of chemokines in the pathogenesis of MCI, and indicate that their levels can be potential biomarkers of the severity of cognitive impairment. For translation of the findings into clinical practice, their validation in larger studies is needed, as well as assessing the associations between chemokine levels and the severity of cognitive impairment in MCI over long-term follow-up.

Keywords: Alzheimer's disease, inflammation, mild cognitive impairment, Montreal Cognitive Assessment, rehabilitation, chemokines

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Introduction

Alzheimer's disease (AD) is the most prevalent neurodegenerative disease in people older than 65 years. The typical morphological attributes of AD include amyloid plaques containing deposits of amyloid-β peptide, neurofibrillary bundles composed of tau protein, and chronic neuroinflammation [4]. An important component of the pathogenesis of neurodegeneration in AD is prolonged activation of innate immune response mechanisms in the central nervous system (CNS) (neuroinflammation), the development and maintenance of which can be facilitated by systemic inflammatory response and immune regulation disorders. In neuroinflammatory conditions, activated microglial cells secrete high levels of free oxygen species, cytokines, chemokines and other inflammatory mediators, which causes neuronal damage, disruption of trophic functions of astrocytes and deposition of neurotoxic amyloid-β oligomers [8].

In a number of cases, the development of AD-type dementia is preceded by mild cognitive impairment (MCI), a clinical condition that is characterized by deficits of memory and other cognitive functions that don't reach the severity of dementia. Patients with MCI have an increased risk of dementia, but a number of patients remain cognitively stable. Neurovisualization and morphological methods detect neurodegeneration in the patients with MCI, and finding new potential prognostic markers in MCI, including immunological markers, is important for clinical practice.

Chemokines are a superfamily of small structurally related cytokines that form a complex network. They normally regulate the movement of white blood cells, but also perform a very wide variety of immune and non-immune functions. Studying the level of chemokines in the MCI patients and its relationship with the clinical manifestations of the disease is a promising area of research, since animal models show that a number of chemokines are involved in the pathogenesis of MCI and AD by stimulating and maintaining neuroinflammation, activation of amyloid-β oligomer deposition and tau protein hyperphosphorylation [7]. Chemokines can be produced not only by innate and adaptive immunity cells, but also by other cells of the body, including CNS cells: microglia, astrocytes, oligodendrocytes, endotheliocytes and neurons [12]. They can contribute to the maintenance of chronic inflammation by attracting T cells to the inflammation focus and activation of mononuclear phagocytes.

The basis of the work was our earlier findings on the associations between systemic inflammation, deficiency of the humoral immune response and progression of cognitive disorders in MCI [10]. The goal of this study was to assess the serum concentrations of chemokines and other inflammatory mediators in patients with mild cognitive impairment undergoing rehabilitation, to study their associations with the severity of cognitive impairment in patients.

Materials and methods

The main study group consisted of 48 patients with mild cognitive decline undergoing medical rehabilitation at the Memory Clinic of Psychiatric Clinical Hospital № 1 (4 men, 44 women, mean age 73.16±2.06 years).

Patients came in with complaints of subjective cognitive impairment, including forgetfulness, attention and concentration deficits, occasional difficulty finding their way home, difficulty expressing thoughts, decreased professional and social productivity, impaired motor skills, and difficulty performing everyday household activities (paying bills, shopping). The rehabilitation course was carried out in face-to-face and half-distance mode under conditions of established restrictions because of COVID-19: face-to-face – once a week (cognitive training and psychotherapy session) and remotely – independent daily performance of tasks by the project participants directed on maintenance and self-rehabilitation of cognitive functions, including use of the developed program of the "Memory Clinic" portal.

Repeated examination of the patients was conducted 6 months after the completion of the rehabilitation course. The duration of the rehabilitation course was 6 weeks, and the total duration of sessions was 96 hours. Rehabilitation was conducted in a group format. The neurocognitive training program was aimed at restoration of visual-spatial recognition, memory, kinesthetic, tactile and somatognostic functions, attention, goal setting, and control functions. Psychotherapy included methods of psychological aid adapted to the rehabilitation program [13].

Patients underwent immunologic studies, clinical evaluation and neuropsychological testing at the starting point of the study and at follow-up. Re-examination was performed 6 months after the initial point.

The control group included 46 healthy volunteers without a diagnosis of MCI, AD or other neurological and psychiatric diseases, and without acute infectious

diseases or systemic diseases in the decompensation phase, comparable with the patients in age and gender.

The study was approved by the local ethics committee of the Kurchatov Institute Research Center. All participants were acquainted with the details of the study and signed a voluntary informed consent sheet, a questionnaire, and a consent to process personal data.

We used a multiplex assay panel (Merck Millipore, Germany) to determine the concentration of cytokines and chemokines in blood serum.

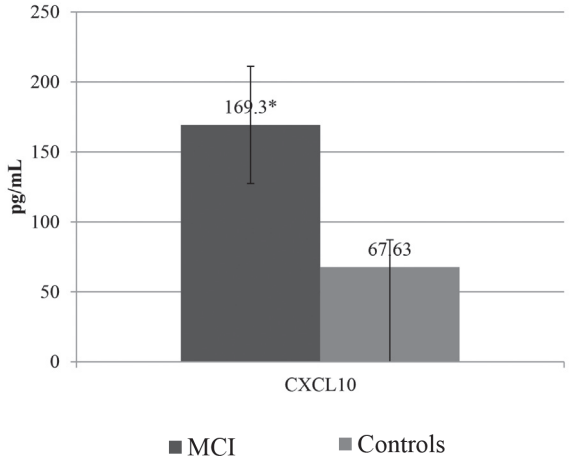

Figure 1. Levels of CXCL10 chemokine in MCI patients and in the control group

Note. *, significant differences with the control group ($p < 0.05$).

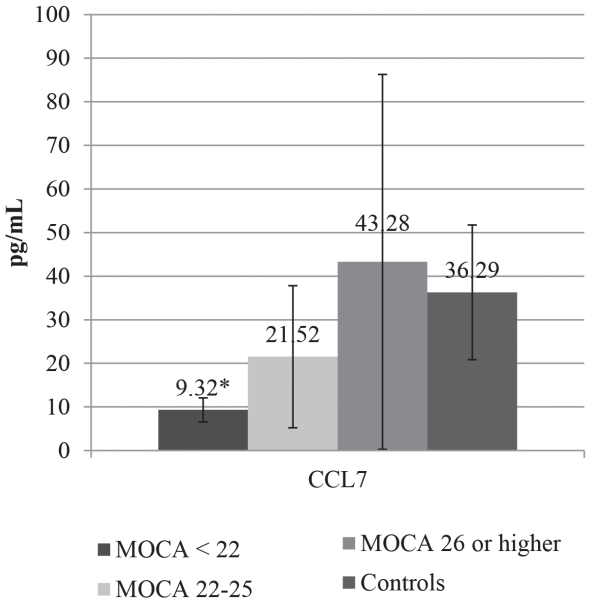

Figure 2. Levels of CCL7 chemokine in MCI patients with different severity of cognitive impairment according to the MOCA scale and in the control group

Note. *, significant differences with the control group ($p < 0.05$).

Cognitive functions were assessed at the Memory Clinic of PKB No. 1 using international neuropsychological scales, including the Montreal Cognitive Scale (MOCA), the Mini Mental Examination Scale (MMSE), the Hospital Anxiety and Depression Scale (HADS), and the clock drawing test.

Excel (Microsoft, 2010) and STATISTICA 10 (StatSoft, 2010) software were used for statistical processing. Normality of distribution was assessed using Shapiro-Wilks criterion. Group results were presented as averages with 95% confidence intervals. Student's t-test was used to assess the significance of differences.

Results and discussion

It was found that levels of the proinflammatory cytokine TNFα (tumor necrosis factor-α), CXCL10/IP10 (interferon-γ inducible protein 10) and MDC (monocyte-derived chemokine, CCL22), which is involved in Th2-link activation of adaptive immunity, were significantly increased in MCI patients (Figure 1, Table 1).

CXCL10/IP10 is a proinflammatory chemokine involved in the effects of cytokine interferon-γ (IFNγ). As reported [2], the content of this chemokine is elevated in the cerebrospinal fluid in Alzheimer's disease in the early stages of dementia and in MCI, and in Alzheimer's disease there is a significant positive correlation between CXCL10 levels and the MMSE score, while in MCI no such correlation was found. Serum CXCL10/IL10 levels in MCI have not previously been studied.

TNFα is one of the major proinflammatory cytokines, secreted mainly by macrophages, NK cells, and lymphocytes. TNFα has 2 receptors, TNFR1 and TNFR2. The TNFR2 receptor is associated with homeostatic functions, whereas activation of the TNFR1 receptor triggers systemic inflammation cascades and causes a wide range of biological effects, including activation of innate immune cells, endothelial activation, acute phase protein synthesis, pyrogenesis, dendritic cell migration to lymph nodes and activation of the adaptive immune response. Depending on the state of the target cell and the microenvironment, TNFα can cause stimulation of survival, proliferative activity of target cells, their necrosis or apoptosis [5]. Increased TNFα levels indicate activation of the systemic inflammatory response in MCI patients, confirming our earlier findings [10]. Data obtained by other researchers also indicate an increase in this cytokine in the blood serum in MCI [15].

MDC is a chemokine expressed by dendritic cells, NK-cells and some T cell subpopulations. The main functions of MDC include the induction

TABLE 1. LEVELS OF CHEMOKINES AND INFLAMMATORY MEDIATORS IN MCI PATIENTS AT BASELINE AND 6 MONTHS AFTER THE REHABILITATION COURSE

Indicator	Baseline	6 months point	Controls
CXCL10, pg/mL	169.3±41.9*, **	75.1±16.6	67.63±19.59
CCL7/MCP-3, pg/mL	21.49±11.51	21.72±10.01	38.81±21.99
TNFα, pg/mL	8.17±1.36**	7.61±2.97	5.57±1.45
MDC, pg/mL	1230.3±323.8*, **	483.1±90.4	597.75±84.74

Note. *, the significance of differences between baseline and the 6 months point, $p < 0.05$; **, the significance of differences with the control group, $p < 0.05$.

and maintenance of activation of the Th2-link of adaptive immunity. This chemokine participates in the pathogenesis of allergic diseases and malignant tumors [11]. According to the literature, increased MDC levels in the cerebrospinal fluid is one of the markers of increased permeability of the blood-brain barrier in AD, which may play an important role in the pathogenesis of AD, contributing to the development and maintenance of chronic neuroinflammation due to violation of the CNS's immuno-privileged status [1].

It was also detected that the content of the interferon-inducible chemokine CCL7/MCP-3 (monocyte chemotactic protein 3) was significantly reduced in MCI patients with a significant degree of cognitive impairment (less than 22 points on the MOCA scale) (n = 13) (Figure 2). The chemokine CCL7 is one of the mediators that promote extravasation of monocytes and neutrophils to the site of the inflammatory reaction. This chemokine is important for the initiation of adaptive immune response to viruses and other intracellular pathogens (*Listeria monocytogenes*, etc.) [14]. Its deficiency leads to impaired monocyte functions, including antigen presentation. The low level of CCL7 in MCI patients with severe cognitive decline may contribute to the deficiency of mechanisms of antigen-dependent cytotoxicity in these patients.

Assessment of the cognitive functions of MCI patients before and after rehabilitation showed that before rehabilitation, the mean MMSE score was 26.08±0.54 and MOCA score was 22.61±0.91. After rehabilitation, the mean MMSE score was 28.18±0.74 ($p = 3.75 \times 10^{-5}$) and MOCA score was 24.00±1.33 ($p > 0.05$). MOCA scores higher than 26 are considered normal and scores from 18 to 25 are characteristic for MCI. For MMSE, scores higher than 26 are considered normal and scores from 18 to 25 are characteristic for MCI. Thus, the rehabilitation course had a favorable effect on the cognitive functions of MCI patients in the short-term dynamics, which was expressed in a significant increase in the MMSE score.

We studied the effect of the rehabilitation course on the level of chemokines and inflammatory mediators in MCI patients. The main results are shown in the Table 1.

It was revealed that at repeated examination after the rehabilitation course in MCI patients the content of proinflammatory cytokine TNFα in blood serum decreased to normal levels, as well as the content of MDC chemokine. MDC, a chemokine that regulates Th2 type of the adaptive immune response and the permeability of BBB. The levels of MDC have been found to increase in the cortex APP/PS1 mice that are susceptible to AD [6]. The decrease of MDC levels in systemic circulation can be beneficial for the patients with MCI, reducing the BBB permeability and neuroinflammation.

It was also found that the content of chemokine CXCL-10/IP-10 (interferon-gamma inducible protein 10) decreased to normal levels after the rehabilitation course. CXCL-10/IP-10 is an important component of the antiviral response, stimulating migration to the site of infection and adhesion of activated type 1 T helpers. CXCL10 is expressed by neurons, glial and stromal cells in various CNS diseases and can play both protective and damaging roles [3]. The chemokine CXCL10 binds to the CXCR3 receptor, which is mainly expressed on activated T cells and natural killer cells. CXCL10 mediates leukocyte influx in various inflammatory diseases of the central nervous system and may be involved in the development of neuroinflammation, contributing to the pathogenesis of Alzheimer's disease [9]. Given the association of the level of this chemokine with the severity of cognitive impairment in MCI, it is of interest to further study it as a marker of the effectiveness of MCI therapy.

Therefore, in this work, we found increase in the levels of several major chemokines that regulate systemic inflammation, cell and humoral mechanisms of adaptive immunity in MCI patients. This increase may reflect activation of inflammation, participate in the development of neuroinflammation, and contribute to the progression of Alzheimer's disease. In particular, we revealed an important fact about the

relationship between the CCL7 chemokine level and the parameters of neuropsychological examination of patients with MCI: decrease in CCL7 content was found to be associated with the severity of cognitive impairment according to the MOCA scale. The findings indicate that decrease in the content of the CCL7 chemokine is a potential marker of the severity of cognitive impairment in MCI.

According to this study, the medical rehabilitation course had a beneficial effect on the cognitive functions of the patients, and was associated with a decrease of the levels of TNFα, CXCL10 and MDC to normal values. These fascinating results show the importance of further research of the influence of medical rehabilitation in MCI on immunological parameters. Some of the factors that can possibly explain these results are a decrease in anxiety, better emotional stability, better organized schedule and higher physical activity in the patients who underwent the rehabilitation course. These factors could have an effect on neuroimmune interactions in the patients, reducing systemic inflammation and the activation of adaptive immunity.

The elevated serum levels of TNFα, CXCL10 and MDC in patients with MCI at the initial examination and their decrease after the rehabilitation course indicate the importance of further study of these proteins as markers of the effectiveness of rehabilitation measures in mild cognitive impairment.

Conclusion

The findings of this study make a contribution to understanding the role of chemokines in the pathogenesis of mild cognitive impairment, and indicate that their levels may be a biomarker of the severity of cognitive decline in patients. It is necessary to validate the obtained data in larger studies, as well as to evaluate the relationship between chemokine levels and the severity of cognitive impairment in MCI in the dynamics of long-term follow-up. Translation of the obtained data and methods into practice is promising for predicting the course of the disease and selection of therapy.

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