DOI: https://doi.org/10.17816/medjrf163238

Роль моноцитов в развитии психовегетативных расстройств у лиц молодого возраста с недифференцированной дисплазией соединительной ткани

И.В. Мальцева, И.И. Шереметьева, Е.Ф. Котовщикова, А.А. Селезнева, Е.В. Буйлова

Алтайский государственный медицинский университет, Барнаул, Россия

АННОТАЦИЯ

Обоснование. Иммунная система играет важную роль в развитии нейропатологии. Нарушение функций моноцитов/макрофагов может способствовать возникновению и развитию нейровоспалительных и нейродегенеративных заболеваний. Выделяют две субпопуляции моноцитов: противовоспалительную и активированную провоспалительную, вырабатывающую цитокины IL-1, IL-6, IL-2, IL-8, TNF-α, которые участвуют в иммунном воспалении при ряде психических заболеваний. Нарушения клеточного, фагоцитарного и/или гуморального звеньев иммунитета часто встречаются у пациентов с недифференцированной дисплазией соединительной ткани (НДСТ). Можно предполагать участие моноцитов в развитии психовегетативных расстройств у пациентов, имеющих соединительнотканную недостаточность.

Цель — изучение взаимосвязи количества моноцитов и провоспалительных цитокинов (IL-1, IL-6, TNF-α) в периферической крови с развитием непсихотических психических расстройств и синдрома вегетативной дисфункции (СВД) при НДСТ у лиц молодого возраста.

Материалы и методы. В исследовании приняли участие 95 человек в возрасте 18–22 лет. Проведены нейропсихологическое обследование, общеклиническое исследование крови, изучались провоспалительные цитокины (IL-1, IL-6, TNF-α), маркёры нейродегенерации (нейронспецифическая енолаза — NSE) и церебральной ишемии (антитела к NR2).

Результаты. Повышение абсолютного числа моноцитов в периферической крови сопровождается меньшей выраженностью психовегетативных, ишемических и нейродегенеративных нарушений. Обнаружена обратная корреляционная связь между уровнем моноцитов в периферической крови и числом баллов НДСТ, прямая — между НДСТ и СВД, астеническим состоянием, личностной тревожностью, депрессией, неврозом, интернет-зависимостью, индексом влияния головной боли на повседневную жизнь. При выраженной НДСТ отмечается изменение соотношения моноцитов в пользу провоспалительной субпопуляции, что, вероятно, является одной из причин большого числа непсихотических психических расстройств и нарушений со стороны вегетативной нервной системы у данной категории пациентов.

Заключение. Повышение числа провоспалительных моноцитов при выраженной НДСТ играет важную роль в развитии психовегетативных нарушений. Коррекция диспластического процесса может стать важным звеном в профилактике и лечении различных неврологических и непсихотических психических расстройств, таких как СВД и тревожно-депрессивный синдром у лиц молодого возраста.

Ключевые слова: моноциты; провоспалительные цитокины; НДСТ; депрессия; церебральная ишемия; нейродегенерация.

Как цитировать

Мальцева И.В., Шереметьева И.И., Котовщикова Е.Ф., Селезнева А.А., Буйлова Е.В. Роль моноцитов в развитии психовегетативных расстройств у лиц молодого возраста с недифференцированной дисплазией соединительной ткани // Российский медицинский журнал. 2023. Т. 29, № 1. С. 5–16. DOI: https://doi.org/10.17816/medjrf163238

Рукопись получена: 31.01.2023 **Рукопись одобрена:** 06.02.2023 **Опубликована:** 28.02.2023

ЭКО•ВЕКТОР

DOI: https://doi.org/10.17816/medjrf163238

Role of monocytes in the development of psychovegetative disorders in young people with undifferentiated connective tissue dysplasia

Irina V. Malceva, Irina I. Sheremetieva, Elena F. Kotovshchikova, Anastasia A. Selezneva, Evgenia V. Buylova

Altai State Medical University, Barnaul, Russian Federation

ABSTRACT

BACKGROUND: The immune system plays an important role in the development of neuropathology. Dysfunction of monocytes/macrophages can contribute to environmental health and the development of neuroinflammatory and neurodegenerative diseases. Two subpopulations of monocytes are distinguished, namely, anti-inflammatory and activated pro-inflammatory monocytes, producing cytokines interleukin (IL)-1, IL-6, IL-2, IL-8, and tumor necrosis factor (TNF)-α, which are involved in immune inflammation in mental diseases. Violations of cellular, phagocytic, and/or humoral immunity are often found in patients with undifferentiated connective tissue dysplasia (UCTD). Monocytes are assumed to be involved in the development of psychovegetative disorders in patients and connective tissue insufficiency.

AIM: To study the relationship between the number of monocytes and pro-inflammatory cytokines (IL-1, IL-6, and TNF-α) in the peripheral blood with possible non-psychotic diseases and autonomic dysfunction syndrome in UCTD in young people.

MATERIALS AND METHODS: We examined 95 people aged 18–22 years. Neuropsychological examination, general clinical blood tests, pro-inflammatory cytokines (IL-1, IL-6, TNF-α), markers of neurodegeneration (neuron-specific enolase) and cerebral ischemia (antibodies to NR2) were sent.

RESULTS: An increase in the absolute monocyte count in the peripheral blood is accompanied by a lesser severity of psychovegetative, ischemic, and neurodegenerative cases. An inverse correlation was found between the level of monocytes in the peripheral blood and the number of UCTD indicators, a direct correlation between UCTD and autonomic dysfunction syndrome (ADS), asthenic condition, personal anxiety, depression, neurosis, Internet addiction, and headache research index for everyday life. Severe UCTD leads to a change in the proportion of monocytes in the use of the pro-inflammatory subpopulation, which is probably one of the reasons for the numerous non-psychotic diseases and autonomic nervous system diseases in these patients.

CONCLUSION: An increase in the pro-inflammatory monocyte count in severe UCTD plays an important role in the development of psychovegetative disorders. The correction of the dysplastic process can become an important role in the prevention and detection of various neurological and non-psychotic diseases, such as ADS and anxiety–depressive syndrome in young people.

Keywords: monocytes; pro-inflammatory cytokines; UCTD; depression; cerebral ischemia; neurodegeneration.

To cite this article

Malceva IV, Sheremetieva II, Kotovshchikova EF, Selezneva AA, Buylova EV. Role of monocytes in the development of psychovegetative disorders in young people with undifferentiated connective tissue dysplasia. *Rossiiskii meditsinskii zhurnal (Medical Journal of the Russian Federation, Russian Journal).* 2023;29(1):5–16. DOI: https://doi.org/10.17816/medjrf163238

Received: 31.01.2023 **Accepted:** 06.02.2023 **Published:** 28.02.2023

ECO•VECTOR

BACKGROUND

Modern research confirms the crucial role of the immune system in the development of central nervous system (CNS) pathologies. Neuroinflammatory and neurodegenerative diseases may be caused by dysfunction of monocytes/macrophages and microglial cells, which perform the function of resident macrophages in the brain parenchyma and are involved in maintaining CNS homeostasis and neurogenesis, neurotrophism, and synaptic remodeling [1, 2].

Peripheral monocytes/macrophages represent a heterogeneous group of cells consisting of two subpopulations, one of which is the subpopulation of classical monocytes, which constitute approximately 95% of peripheral blood monocytes. The remaining monocytes, the nonclassical ones, are proinflammatory, since they implement inflammatory reactions, participate in the mechanisms of development of chronic inflammation, and are characterized by increased secretion of chemokines and biologically active proinflammatory cytokines, namely, interleukin (IL)-1, IL-6, IL-8, IL-12, and tumor necrosis factor α (TNF-α) and receptors, and therefore, based on the level of these proinflammatory marker level, the predominance of a certain subpopulation of monocytes can be indirectly determined [1–3].

The counts of active circulating monocytes/macrophages has been found to increase in patients with mental disorders, and as a result of disruption of the integrity of the blood–brain barrier, they migrate to the CNS [4–6]. Activated monocytes/macrophages and microglial cells intensively synthesize proinflammatory cytokines, which play a critical role in immune inflammation, which destabilizes the brain, causes neuronal degeneration, and with the participation of certain environmental factors and genetic predisposition, can cause the development of mental disorders, which has been proven in relation to schizophrenia, bipolar affective disorder, and depression [2, 3, 7–9].

Depression is a severe multifactorial disease associated with various brain processes, including synaptic dysfunction and neuroinflammation. Immune inflammation in the pathogenesis and etiology of depression is evidenced by an increase in the counts of proinflammatory subpopulations of monocytes, neutrophils, activated T lymphocytes, and inflammatory cytokine (IL-l, IL-2, IL-6, IL-8, TNF-α) secretion, inducing changes in the metabolism of monoamines, which leads to dopamine, norepinephrine, and serotonin deficiency, which is considered a main causes of depression [5]. Previous studies have shown the participation of chemokines, also secreted by monocytes, in neuroendocrine function, neurotransmission, and neurodegeneration and the inclusion of a proapoptotic cascade [2], which confirms the critical role of the monocyte component of immunity in the development of various mental and neurological diseases.

The syndrome of immunological disorders, including insufficiency of the cellular, phagocytic, and/or humoral components of the immune system, is often found in patients with undifferentiated connective tissue dysplasia (UCTD) [10]. Moreover, up to 90% of UCTD patients have neurological and/or mental disorders, such as autonomic nervous system dysfunction, asthenic conditions, neurotic disorders, hypochondria, anxiety and depressive syndromes, and behavioral disorders [10, 11]. It can be assumed that monocytes/macrophages and proinflammatory cytokines are involved in the development of psychovegetative disorders in patients with connective tissue deficiency.

This study aimed to analyze the relationship between the counts of monocytes and proinflammatory cytokines (IL-1, IL-6, and TNF-α) in the peripheral blood and the development of nonpsychotic mental disorders and autonomic dysfunction syndrome in UCTD in young people.

MATERIALS AND METHODS

Study design

An observational, single-center, prospective, full-design study was conducted.

Compliance criteria

The study was completed in two stages. At stage 1, 212 students studying at the Altai State Medical University were evaluated. Inclusion criteria were age of 18–22 years and signed informed consent. The noninclusion criteria for this group were organic brain diseases, a history of psychotic mental disorders, acute and chronic somatic diseases in the stage of decompensation, and intake of antidepressants.

At stage 2, the study included 95 patients comparable in age, sex, and severity of UCTD with the groups of stage 1.

Conditions

The study was conducted by Professor Barkagan from the Department of Propaedeutics of Internal Diseases, Altai State Medical University (Barnaul).

Study duration

The duration of the study was 3 months.

Description of medical intervention

The present study used the following research methods. At stage 1, the severity of UCTD was determined using a scoring scale for the significance of phenotypic criteria with an assessment of the total score by Kadurina (2009). This scale was proposed to determine the severity of UCTD in children and adolescents and is widely used in pediatrics. However, for patients aged 18 years, there is still no confirmed list of diagnostic criteria for UCTD; there is no generally accepted diagnostic algorithm and diagnostic threshold for scoring connective tissue insufficiency. To distribute the participants according to the severity of UCTD, we set point criteria: >17 points and <39 points, moderate, and ≥39 points, severe. To verify and quantify the manifestations

of psychovegetative syndrome, generally accepted methods were used, namely, Vein's questionnaire to identify signs of autonomic disorders (autonomic dysfunction syndrome, ADS), Malkova's scale of asthenic state (adapted by Chertova) to assess the severity of asthenia, and Spielberger–Hanin's test to determine situational and personal anxiety. The presence of depression and its level were assessed using the Beck Depression Inventory, and the effect of headache on daily activity was analyzed using the HIT-6 index. Moreover, Hall's technique was used to assess emotional intelligence and the Heck–Hess test to evaluate the probabilities of neurosis. Additionally, typological personality traits were determined using Jung's test; Kraepelin's technique was used to assess mental performance, and a questionnaire to determine Internet addiction was applied.

At stage 2, a general clinical blood test was performed. IL-1, IL-6, TNF-α, neuron-specific enolase (NSE) levels were determined using reagents from Vector (Russia), and the level of antibodies to NR2 (NR2-At) was determined using the NR2-AT-ELISA reagent kit (DRD, Russia).

Statistical analysis

Empirical data distributions were tested for agreement with the law of normal distribution using the Shapiro–Wilk test. Because of the nonnormal distribution of data, the nonparametric Mann–Whitney *U* rank test was used to compare continuous indices between groups. Descriptive characteristics are presented as median (Me [Q1; Q3]) for numerical data and quantities (percentage) for categorical data. Fisher's exact two-tailed test was used to compare categorical and binary indices. Pairwise relationships between indicators were identified by calculating the Spearman correlation coefficient. The study of the relationships between the indicators under consideration was conducted by constructing single-factor linear regression models. Differences were considered statistically significant at $p < 0.05$. Statistical calculations were performed using the RStudio program in the R language (version 4.0.2).

Ethical considerations

This study was approved by the local ethics committee of Altai State Medical University (protocol no. 9; November 27, 2018).

RESULTS

According to the criteria for determining UCTD, among 212 students, moderate UCTD was detected in 121 (57%) cases, severe UCTD was revealed in 59 respondents (28%), and the total score of external phenotypic manifestations of connective tissue insufficiency was <17 points in 32 patients (15%).

At stage 2, the study included 95 patients comparable in age, sex, and severity of UCTD with the groups in stage 1.

Table 1 presents the comparative characteristics of UCTD indicators, psychovegetative status, proinflammatory cytokines (IL-1, IL-6, and TNF-α), markers of cerebral ischemia (NR2-At), and neurodegeneration (NSE) in patients with different monocyte concentrations.

An increase in the counts of monocytes in the blood is associated with a lower number of disorders of psychovegetative status, as evidenced by lower scores of autonomic dysfunction, asthenia, depression, neurosis, index of the impact of headache on daily life, Internet addiction, and higher rates of emotional intelligence and mental performance. An inverse correlation was noted between the level of monocytes in the peripheral blood and the asthenic state scores (r=–0.23; p=0.033), the index of the impact of headache on daily life (r=–0.27; p=0.030), and magnesium level in the blood (r=0.39; $p < 0.001$). Moreover, the differences were more pronounced in the group with an absolute increase in the production of monocytes by the bone marrow than in the group with a relative redistribution of leukocytes in favor of monocytes.

UCTD is characterized by the development of immunological disorders in which monocytes/macrophages play a crucial role with lymphocytes and plasma cells. The present study included 15 patients without UCTD (group 0), 38 patients with moderate and severe UCTD (group 1), and 42 students (group 2) (Table 2).

Table 2 shows that psychovegetative disorders increase as the UCTD scores increase. With a general decrease in monocytes in the group with severe UCTD, the level of inflammatory markers was higher than in the group with moderate dysplasia, which may indicate the predominance of the proinflammatory subpopulation of monocytes in the case of severe connective tissue inadequacy. The increase in antiinflammatory monocytes in the moderate UCTD group may be a manifestation of adaptive mechanisms aimed at restoring mental health, whereas the depletion of adaptive resources in severe UCTD is accompanied by both a decrease in the production of monocytes and an increase in the activity of inflammatory processes. An inverse correlation was detected between the level of monocytes in the peripheral blood and the UCTD score (r=–0.25; p=0.017), and a direct correlation was noted between UCTD and ADS (r=0.55; $p < 0.001$), asthenic state (r=0.4; $p < 0.001$), personal anxiety (r=0.14; p=0.048), depression (r=0.33; $p < 0.001$), neurosis (r=0.18; p=0.016), Internet dependence (r=0.29; $p < 0.001$), and the index of the impact of headache on everyday life (r=0.31; p=0.001).

Figure 1 presents the distribution of the severity of connective tissue deficiency at different monocyte levels in the blood. Among the students who had pronounced UCTD, absolute monocytosis was not detected.

Our study did not detect any differences between the counts of monocytes and the level of TFN-α and IL-1 in students without depression (n=50) and in those with depression of varying severity (n=45) (Table 3). This may be due to the probable short history of depressive disorder in students, as several studies have not revealed differences

Table 1. Indicators of undifferentiated connective tissue dysplasia, psychovegetative status, and blood in patients with different levels of monocytes, Me [Q1; Q3]

Indicators	Monocyte count ≤0.8×10⁹/L (*n*=86)	Monocyte count >0.8×10⁹/L (*n*=9)	*p*	Monocyte count ≤9% (*n*=65)	Monocyte count >9% (*n*=30)	*p*
Monocytes, 10^9/l	0.40 [0.40; 0.55]	1.0 [0.9; 1.7]	0.0001*	0.4 [0.3; 0.5]	0.6 [0.5; 0.8]	0.0002*
Monocytes, %	7.4 [6.0; 9.2]	15.8 [10.5; 28.2]	0.0002*	6.5 [5.6; 8.0]	10.5 [9.5; 11.3]	0.001*
UCTD, points	38.0 [26.3; 45.0]	34.0 [22.0; 35.0]	0.167	39.0 [29.0; 45.0]	32.5 [25.0; 43.0]	0.165
ADS, points	32.0 [20.0; 43.0]	23.0 [14.0; 30.0]	0.049*	36.0 [18.5; 43.5]	27.0 [22.0; 36.0]	0.141
Asthenic state, points	52.0 [46.0; 66.0]	46.0 [37.0; 53.0]	0.075	51.5 [45.5; 65.0]	52.0 [45.0; 63.0]	0.584
Situational anxiety, points	42.0 [34.0; 51.0]	43.0 [34.0; 54.0]	0.677	42.0 [35.0; 52.0]	42.5 [34.0; 48.5]	0.533
Personal anxiety, points	48.0 [40.0; 53.0]	45.0 [44.0; 49.0]	0.642	49.0 [41.0; 53.0]	45.5 [40.0; 53.0]	0.642
Depression, points	13.0 [7.0; 23.0]	9.0 [7.0; 14.0]	0.263	13.5 [6.0; 22.0]	11.5 [7.0; 20.0]	0.650
Headache index, points	51.0 [44.0; 62.0]	48.0 [42.0; 55.0]	0.546	54.0 [45.0; 63.0]	46.5 [42.0; 56.0]	0.030*
Emotional intelligence (sum), points:	38.0 [26.0; 52.0]	43.0 [35.0; 62.0]	0.232	38.0 [26.5; 53.0]	39.0 [21.0; 53.0]	0.755
emotional awareness, points	10.0 [7.0; 14.0]	13.0 [12.0; 16.0]	0.031*	11.0 [8.0; 14.0]	10.0 [7.0; 16.0]	0.785
Internet addiction, points	28.0 [18.0; 38.0]	17.0 [12.0; 24.0]	0.034*	24.5 [16.0; 37.0]	24.0 [20.0; 35.0]	0.913
Neurosis, points	20.0 [14.0; 27.0]	14.0 [13.0; 21.0]	0.139	20.0 [13.0; 26.5]	19.0 [14.0; 23.0]	0.872
Intro/ambo/extraversion, points	45.0 [35.0; 60.0]	60.0 [55.0; 60.0]	0.053	45.0 [40.0; 60.0]	50.0 [32.5; 60.0]	0.888
Mental performance, points:						
Counting rate, number of characters	90.0 [77.0; 119.0]	103.0 [74.0; 128.0]	0.736	90.0 [76.0; 119.0]	95.0 [77.0; 119.0]	0.978
Coefficient of attention switching, units	0.86 [0.79; 0.93]	0.96 [0.94; 1.0]	0.005*	0.88 [0.80; 0.93]	0.85 [0.79; 0.94]	0.921
Efficiency factor, units	0.9 [0.8; 1.0]	0.91 [0.9; 1.0]	0.840	0.89 [0.82; 0.97]	0.92 [0.84; 1.08]	0.305
NR2-At, ng/ml	2.8 [1.9; 5.3]	1.6 [1.3; 4.1]	0.217	2.8 [1.9; 4.8]	2.6 [1.5; 5.7]	0.703
NSE, ng/ml	3.0 [2.1; 4.1]	1.7 [1.5; 3.3]	0.217	3.3 [2.2; 5.0]	2.1 [1.5; 2.9]	0.002*
TNF-α, pg/ml	3.6 [2.8; 4.4]	2.01 [1.50; 2.70]	0.042*	3.6 [2.8; 4.4]	3.0 [2.6; 4.4]	0.140
IL-1, pg/ml	1.7 [1.5; 2.2]	1.45 [1.40; 1.50]	0.049*	1.7 [1.5; 2.3]	1.5 [1.4; 1.8]	0.043*
IL-6, pg/ml	1.03 [0.50; 2.20]	0.88 [0.28; 1.0]	0.315	1.3 [0.6; 2.3]	0.68 [0.38; 0.97]	0.007*

Note: UCTD, undifferentiated connective tissue dysplasia; ADS, autonomic dysfunction syndrome; NSE, neuron-specific enolase; TNF-α, tumor necrosis factor α; IL, interleukin; * statistically significant differences between groups.

Table 2. Indicators of psychovegetative status and blood in undifferentiated connective tissue dysplasia, Me [Q1; Q3]

Indicators	Group 0 without UCTD (*n*=15)	Group 1 with moderate UCTD (*n*=38)	Group 2 with pronounced UCTD (*n*=42)	*p*
UCTD, points	13.0 [9.0; 15.0]	29.0 [25.0; 33.0]	45.0 [41.0; 49.0]	p_{0-1} <0.001* p_{0-2} <0.001* p_{1-2} <0.001*
ADS, points	16.0 [10.5; 26.0]	31.0 [22.0; 41.0]	40.5 [31.0; 49.0]	p_{0-1} <0.001* p_{0-2} <0.001* p_{1-2} <0.001*
Asthenic state, points	43.0 [37.0; 48.0]	51.0 [44.0; 61.0]	59.50 [50.25; 69.0]	p_{0-1}=0.004* p_{0-2} <0.001* p_{1-2}=0.002*
Situational anxiety, points	35.0 [30.0; 45.5]	45.0 [36.0; 51.0]	43.5 [36.0; 49.5]	p_{0-1}=0.053 p_{0-2}=0.090 p_{1-2}=0.775
Personal anxiety, points	45.0 [39.0; 51.5]	48.50 [39.75; 53.0]	49.0 [43.25; 54.0]	p_{0-1}=0.650 p_{0-2}=0.263 p_{1-2}=0.423
Depression, points	6.0 [3.0; 16.5]	12.0 [7.0; 17.75]	17.5 [11.0; 23.0]	p_{0-1}=0.068 p_{0-2}=0.005* p_{1-2}=0.009*
Headache impact index, points	46.0 [38.0; 50.0]	50.0 [44.75; 59.0]	55.0 [45.0; 62.0]	p_{0-1}=0.071 p_{0-2}=0.029* p_{1-2}=0.394
Internet addiction, points	19.0 [15.0; 24.0]	23.0 [14.0; 33.0]	30.0 [23.0; 40.5]	p_{0-1}=0.270 p_{0-2}=0.015* p_{1-2}=0.023*
Monocytes, 10^9/L	0.5 [0.4; 0.6]	0.5 [0.4; 0.7]	0.4 [0.3; 0.5]	p_{0-1}=0.629 p_{0-2}=0.152 p_{1-2}=0.013*
Monocytes, %	7.5 [6.0; 9.3]	8.8 [6.6; 20.5]	7.3 [5.2; 8.8]	p_{0-1}=0.312 p_{0-2}=0.510 p_{1-2}=0.019*
TNF-α, pg/ml	4.2 [3.0; 5.0]	3.1 [2.5; 4.4]	3.7 [3.0; 4.0]	p_{0-1}=0.117 p_{0-2}=0.391 p_{1-2}=0.138
IL-1, pg/ml	2.0 [1.6; 2.1]	1.5 [1.4; 1.7]	1.8 [1.5; 2.3]	p_{0-1}=0.004* p_{0-2}=0.703 p_{1-2}=0.016*
IL-6, pg/ml	1.1 [0.9; 2.9]	0.68 [0.4; 1.9]	1.3 [0.6; 2.2]	p_{0-1}=0.059 p_{0-2}=0.981 p_{1-2}=0.081

Note: UCTD, undifferentiated connective tissue dysplasia; ADS, autonomic dysfunction syndrome; TNF-α, tumor necrosis factor α; IL, interleukin; * statistically significant differences between groups.

in IL-1, IL-6, and IL-10 concentrations in patients with an initial episode of depression [2, 3]. Moreover, in our study, the IL-6 level in the group with severe (according to the Beck questionnaire) depression was 40% higher (1.26 pg/ml versus 0.89 pg/ml); however, the differences were not statistically significant.

The number of students with severe depression was significantly lower both in the group with relative and in the group with absolute monocytosis (Fig. 2).

As a result of studying situational and personal anxiety, a general trend toward a decrease in the level of monocytes and inflammatory markers (except for TNF-α) was noted in groups with high anxiety of both types compared with those with moderate (normal) anxiety; however, the differences were not statistically significant in all cases. Notably, more than half of the students had a high level of personal anxiety, which is an individual stable characteristic that reflects the participant's predisposition to anxiety and may indicate mental maladjustment.

In our study, we studied a reliable marker of cerebral ischemia, namely, antibodies to the NR2 subunit, in which an increase of more than 2 ng/ml indicates a history of single or repeated episodes of cerebral ischemia over the past 3–6 months. This marker was elevated in 71% of students, indicating a high incidence of cerebral blood flow disorders among patients aged 18–22 years. Because the students included in the study did not have clinical manifestations of acute cerebral ischemia (acute cerebrovascular accident, transient ischemic attack), we can suggest laboratory-confirmed cases of asymptomatic subclinical cerebral ischemia or the onset of chronic cerebral ischemia.

In students with elevated levels of antibodies to NR2 (*n*=67), the absolute counts of monocytes were significantly lower than those in individuals who did not have cerebral ischemia (*n*=28) (Table 4), whereas the concentration of proinflammatory cytokines was practically the same. This may indicate a decrease in the counts of classical monocytes and a lack of growth of nonclassical activated monocytes in the case of subclinical cerebral ischemia.

With absolute monocytosis, the number of students without cerebral ischemia was significantly less than those

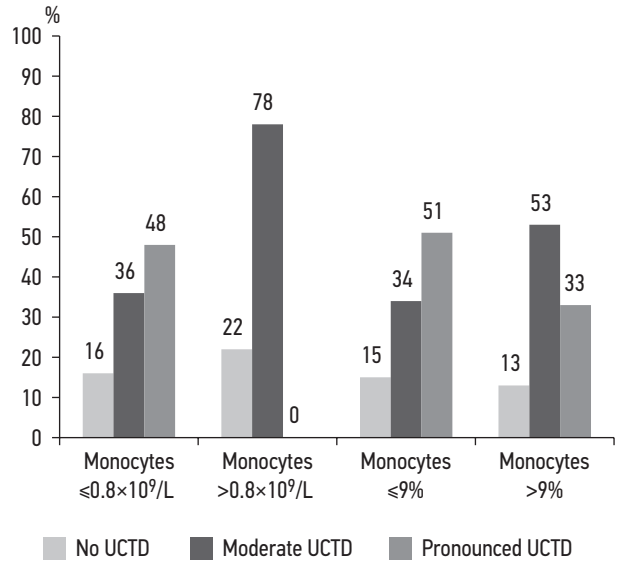

Fig. 1. Distribution of undifferentiated connective tissue dysplasia in different levels of monocytes, %.

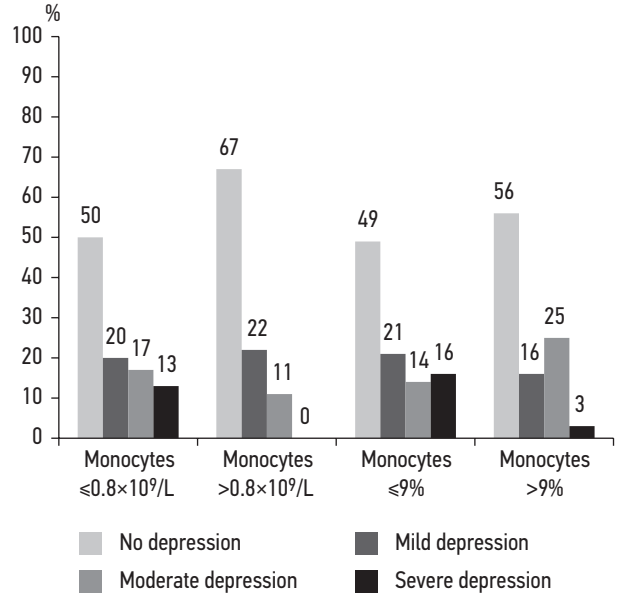

Fig. 2. Distribution of depression in different levels of monocytes.

Table 3. Monocyte count and pro-inflammatory cytokine level in depression, Me [Q1; Q3]

Indicators	No depression (*n*=50)	Depression (*n*=45)	*p*
Depression, points	7.0 [4.0; 10.0]	21.0 [17.5; 27.5]	<0.0001*
Monocytes, 10^9/l	0.5 [0.4; 0.6]	0.45 [0.30; 0.55]	0.367
Monocytes, %	8.1 [6.3; 9.8]	7.5 [5.8; 9.3]	0.432
TNF-α, pg/ml	3.6 [2.7; 4.6]	3.2 [2.7; 4.1]	0.249
IL-1, pg/ml	1.6 [1.5; 2.0]	1.6 [1.4; 2.2]	0.716
IL-6, pg/ml	0.9 [0.4; 2.1]	1.1 [0.5; 1.9]	0.478

Note: TNF-α, tumor necrosis factor α; IL, interleukin; * statistically significant differences between groups.

Table 4. Monocyte count and pro-inflammatory cytokine level in brain ischemia, Me [Q1; Q3]

Indicators	Antibodies to NR2 ≤2 ng/ml (*n*=28)	Antibodies to NR2 >2 ng/ml (*n*=67)	*p*
Antibodies to NR2, ng/ml	1.4 [1.2; 1.7]	4.1 [2.7; 5.6]	<0.0001*
Monocytes, 10^9/l	0.5 [0.5; 0.7]	0.4 [0.3; 0.6]	0.018*
Monocytes, %	8.3 [6.9; 10.5]	7.6 [6.1; 9.5]	0.229
TNF-α, pg/ml	3.4 [2.8; 4.3]	3.5 [2.6; 4.4]	0.836
IL-1, pg/ml	1.6 [1.5; 2.0]	1.7 [1.4; 2.1]	0.869
IL-6, pg/ml	0.8 [0.4; 1.4]	0.98 [0.50; 2.0]	0.330

Note: TNF-α, tumor necrosis factor α, IL, interleukin; * statistically significant differences between groups.

Table 5. Monocyte count and pro-inflammatory cytokine level in different levels of neurodegeneration. Me [Q1; Q3]

Indicators	NSE ≤3.5 ng/ml (*n*=59)	NSE >3.5 ng/ml (*n*=36)	*p*
NSE, ng/ml	2.15 [1.60; 2.70]	4.98 [3.90; 5.80]	<0.0001*
Monocytes, 10^9/L	0.5 [0.4; 0.6]	0.4 [0.3; 0.5]	0.048*
Monocytes, %	8.2 [6.6; 9.3]	6.1 [5.1; 8.0]	0.001*
TNF-α, pg/ml	3.6 [2.9; 4.4]	4.0 [3.1; 4.9]	0.102
IL-1, pg/ml	1.6 [1.4; 1.9]	1.9 [1.5; 2.5]	0.013*
IL-6, pg/ml	0.76 [0.38; 1.60]	1.4 [0.7; 4.0]	0.011*

Note: NSE, neuron-specific enolase. TNF-α, tumor necrosis factor α. IL, interleukin; * statistically significant differences between groups.

who had an increased level of the studied marker (Fig. 3), which confirms the neuroprotective effect of this type of leukocyte. A negative correlation was noted (r=–0.32; p=0.007). Furthermore, a statistically significant increase in the titer of a marker of cerebral ischemia was established

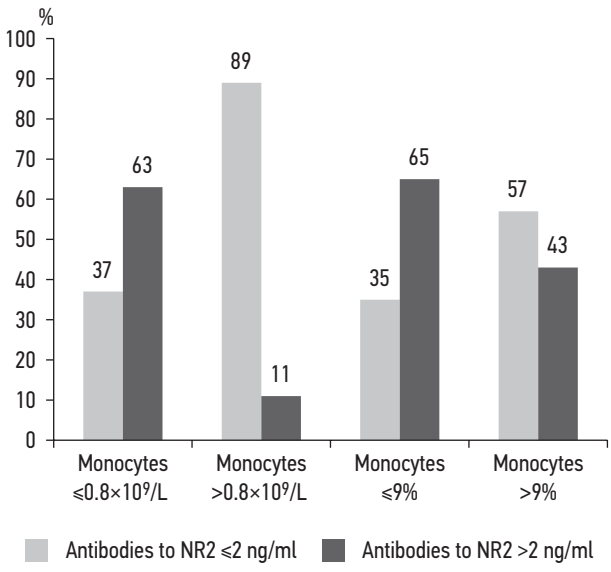

Fig. 3. Distribution of the biomarker of brain ischemia in students with different levels of monocytes.

in the group with severe UCTD compared with the group of participants without dysplastic phenotypic signs (3.7 ng/ml and 2.2 ng/ml, respectively; p=0.012), whereas the number of patients with a history of cerebral ischemia increased as the severity of the dysplastic process increased, reaching almost fourfold predominance in the group with severe UCTD. In the group with moderate and severe UCTD, the correlation was inversely mean (r=–0.56 and –0.54, respectively) and statistically significant in the group with moderate dysplasia. Additionally, when constructing univariate logistic regression models, one of the predictors associated with an increase in the possibility of cerebral ischemia was the presence of UCTD (odds ratio, 2.12; p=0.024).

Among the examined students, the neuron destruction marker NSE was within the reference values, despite the large number of psychovegetative disorders and high incidence of ischemic events in the CNS. We believe that in the long term, neurodegeneration severity may have a crucial prognostic value for the development of neurological and/or mental diseases; therefore, we divided the participants into two groups according to NSE level, in one of which the concentration of this marker was <3.5 ng/ml (n=59), whereas in another group (n=36), it was above this level (Table 5).

In the group with higher NSE level, both the absolute and relative levels of monocytes were significantly lower,

whereas the inflammatory marker (IL-1 and IL-6) levels were higher. The correlation between NSE and monocyte count was r=0.33 (p=0.007), r=0.31 (p=0.007) for TNF-α, r=0.5 (<0.001) for IL-1, and r=0.55 (p <0.001) for IL-6.

DISCUSSION

In the absence of acute and exacerbation of chronic diseases, monocytes with antiinflammatory properties predominate in the peripheral blood, which is confirmed by significantly lower proinflammatory cytokine (IL-1, IL-6, and TNF-α) levels. These monocytes/macrophages have protective properties in relation to the CNS, as evidenced by the lower severity of psychovegetative disorders and lower levels of markers of cerebral ischemia and neurodegeneration in the peripheral blood.

As the phenotypic manifestations of UCTD increase, nonpsychotic mental disorders (anxiety and depression) and autonomic nervous system disorders increase, which probably, with moderate UCTD, leads to the activation of compensation mechanisms, one of which is an increase in the count of antiinflammatory monocytes. With severe UCTD, adaptive reserves are depleted, which is accompanied by a decrease in the absolute count of monocytes and a redistribution of existing monocytes toward a subpopulation of activated proinflammatory cells, which, under conditions of the blood–brain barrier periodically opening because of single or repeated subclinical ischemic events, are involved in neuroinflammatory and neurodegenerative processes in the CNS. Apparently, subclinical cerebral ischemia does not cause a pronounced inflammatory reaction; however, it promotes the penetration of monocytes/macrophages into the CNS, which then, depending on their direction, participate in neuroregeneration or immune inflammation. One of the possible causes of the increase in counts of proinflammatory monocytes/macrophages in the peripheral blood in patients with severe UCTD may be the active degradation of the fibrillar structures of the intercellular substance, particularly collagen fibers. A similar mechanism was discovered in the early stages of atherosclerotic plaque formation, when the activation and directed migration of monocytes, which underlies the development of immune inflammation, is regulated by the degradation products of fibrin and collagen of the vascular wall [1].

Microglial cells are resident macrophages in the CNS and, having a common mesenchymal origin with monocytes, can also be involved in the pathological process in UCTD, reducing the regenerative potential of the nervous tissue. Monocytes/macrophages actively interact with microglia through the blood–cerebrospinal fluid barrier, cerebrospinal fluid–encephalitic barrier (norm), and blood–brain barrier damaged because of ischemia [12–16]. Quantitative and qualitative changes in monocytes in the peripheral blood possibly influence and reflect the state of microglial cells in the CNS. Furthermore, antiinflammatory monocytes/macrophages, which have potent reparative effects on nervous tissue, are candidates for the treatment of various neurological and psychiatric diseases [17].

CONCLUSION

Increased antiinflammatory monocyte levels in the peripheral blood have a protective effect on the CNS, which is expressed in the prevention of psychovegetative, ischemic, and neurodegenerative disorders. This may be because classical monocytes from the peripheral blood are polarized into antiinflammatory macrophages, which have neuroregenerative and antiinflammatory effects.

Nonpsychotic mental disorders (e.g., anxiety, depression) and autonomic nervous system disorders with severe UCTD may be associated with insufficient antiinflammatory monocyte production; therefore, correction of the dysplastic process is crucial for treating various psychovegetative diseases.

ADDITIONAL INFORMATION

Funding source. This study was not supported by any external sources of funding.

Competing interests. The authors declare that they have no competing interests.

Author's contribution: I.V. Malceva — conception, search for literary sources, manuscript writing, and editing; I.I. Sheremetieva — scientific advice; E.F. Kotovshchikova — manuscript editing; A.A. Selezneva — search for literary sources; E.V. Buylova — collaboration of authors and approval of the final manuscript. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

REFERENCES

1. Vasilyeva EF, Brusov OS. The role of monocytes cellular and molecular mechanisms in the development of systemic immune inflammation. Part 1. *Psychiatry (Moscow).* 2020;18(3):76–85. (In Russ). doi: 10.30629/2618-6667-2020-18-3-76-85

2. Vasilyeva EF, Brusov OS. Cellular and molecular mechanisms of proinflammatory monocytes participation in the pathogenesis of mental disorders. Part 2. *Psychiatry (Moscow).* 2020;18(4):81–92. (In Russ). doi: 10.30629/2618-6667-2020-18-4-81-92

3. Vasilyeva EF, Sekirina TP, Sarmanova ZV, et al. Estimation of level of subpopulation CD14+, CD16+ monocytes in patients with juvenile depressions. *Medical Immunology (Russia).* 2019;21(2): 257–258. (In Russ). doi: 10.15789/1563-0625-2019-2-257-268

4. Merino A, Buendia P, Martin-Malo A, et al. Senescent CD14+, CD16+ monocytes exhibit proinflammatory and proatherosclerotic activity. *J Immunol.* 2011;186(3):1809–1815. doi: 10.4049/jimmunol.1001866

5. Strauss-Ayali D, Conrad SM, Mosser DM. Monocyte subpopulations and their differentiation patterns during infection. *J Leukoc Biol*. 2007;82(2):244–252. doi: 10.1189/jlb.0307191
6. Theodoropoulou S, Spanakos G, Baxevanis CN, et al. Cytokine serum levels, autologous mixed lymphocyte reaction and surface marker analysis in never medicated and chronically medicated schizophrenic patients. *Schizophr Res*. 2001;47(1):13–25. doi: 10.1016/s0920-9964(00)00007-4
7. Takahashi V, Yu Z, Sakai M, Tomita H. Linking activation of microglia and peripheral monocytic cells to the pathophysiology of psychiatric disorders. *Front Cell Neurosci*. 2016;10:144. doi: 10.3389/fncel.2016.00144
8. Talarowska M, Szemraj J, Gałecki P. The role of interleukin genes in the course of depression. *Open Med (Wars)*. 2016;11(1):41–48. doi: 10.1515/med-2016-0009
9. Aleshkina GA, Bardenshtejna LM. *Ostrye i prehodjashhie psihoticheskie rasstrojstva*. ID «Medpraktika-M»; 2017. 180 p. (In Russ).
10. Undifferentiated connective tissue dysplasia (the project of guidelines). *Therapy*. 2019;5(7):9–42. (In Russ). doi: 10.18565/therapy.2019.7.9-42
11. Nechaykina SA, Malmberg SA, Petrukhin AS. Neurologic disorders associated with dysplasia of connective tissue in children and their correction. *Russian Journal of Child Neurology*. 2010;5(3):11–20. (In Russ).
12. Alekseeva OS, Kirik OV, Gilerovich EG, Korzhevskii DE. Microglia of the brain: origin, structure and functions. *Zhurnal evolyutsionnoi biokhimii i fiziologii*. 2019;55(4):231–241. (In Russ). doi: 10.1134/S0044452919040028
13. Gogoleva VS, Drutskaya MS, Atretkhany KS-N. The role of microglia in the homeostasis of the central nervous system and neuroinflammation. *Molecular Biology*. 2019;53(5):696–703. (In Russ). doi: 10.1134/S0026898419050057
14. Nikiforova (Postnikova) TA, Peskov SA, Doronina OB. Analysis of the modern status of clinical and experimental data about interaction between nervous and immune systems. *Bulletin of Siberian Medicine*. 2014;13(6):72–80. (In Russ).
15. Zhao M, Tuo H, Wang S, Zhao L. The roles of monocyte and monocyte-derived macrophages in common brain disorders. *Biomed Res Int*. 2020;2020:9396021. doi: 10.1155/2020/9396021
16. Chernykh ER, Shevela EY, Ostanin AA. The role of macrophages in damage recovery of central nervous system: new options for treatment of neurological disorders. *Medical Immunology (Russia)*. 2017;19(1):7–18. (In Russ). doi: 10.15789/1563-0625-2017-1-7-18
17. Sakhno LV, Shevela EYa, Chernykh ER. Phenotypic and functional characteristics of the alternative activated macrophages: potential use in regenerative medicine. *Immunologiya*. 2015;36(4): 242–246. (In Russ).

СПИСОК ЛИТЕРАТУРЫ

1. Васильева Е.Ф., Брусов О.С. Роль моноцитов в клеточно-молекулярных механизмах развития системного иммунного воспаления. Часть 1 // Психиатрия. 2020. Т. 18, № 3. С. 76–85. doi: 10.30629/2618-6667-2020-18-3-76-85
2. Васильева Е.Ф., Брусов О.С. Клеточно-молекулярные механизмы участия провоспалительных моноцитов в патогенезе психических расстройств. Часть 2 // Психиатрия. 2020. Т. 18, № 4. С. 81–92. doi: 10.30629/2618-6667-2020-18-4-81-92
3. Васильева Е.Ф., Секирина Т.П., Сарманова З.В., и др. Оценка уровня субпопуляции моноцитов CD14+/CD16+ у больных юношескими депрессиями // Медицинская иммунология. 2019. Т. 21, № 2. С. 257–268. doi: 10.15789/1563-0625-2019-2-257-268
4. Merino A., Buendia P., Martin-Malo A., et al. Senescent CD14+CD16+ monocytes exhibit proinflammatory and proatherosclerotic activity // J Immunol. 2011. Vol. 186, N 3. P. 1809–1815. doi: 10.4049/jimmunol.1001866
5. Strauss-Ayali D., Conrad S.M., Mosser D.M. Monocyte subpopulations and their differentiation patterns during infection // J Leukoc Biol. 2007. Vol. 82, N 2. P. 244–252. doi: 10.1189/jlb.0307191
6. Theodoropoulou S., Spanakos G., Baxevanis C.N., et al. Cytokine serum levels, autologous mixed lymphocyte reaction and surface marker analysis in never medicated and chronically medicated schizophrenic patients // Schizophr Res. 2001. Vol. 47, N 1. P. 13–25. doi: 10.1016/s0920-9964(00)00007-4
7. Takahashi V., Yu Z., Sakai Mai., Tomita H. Linking activation of microglia and peripheral monocytic cells to the pathophysiology of psychiatric disorders // Front Cell Neurosci. 2016. Vol. 10. P.144. doi: 10.3389/fncel.2016.00144
8. Talarowska M., Szemraj J., Gałecki P. The role of interleukin genes in the course of depression // Open Med (Wars). 2016. Vol. 11, N 1. P. 41–48. doi: 10.1515/med-2016-0009
9. Алешкина Г.А., Барденштейна Л.М. Острые и преходящие психотические расстройства. ИД «Медпрактика-М», 2017. 180 с.
10. Акатова Е.В., Аникин В.В., Арсентьев В.Г., и др. Недифференцированные дисплазии соединительной ткани (проект клинических рекомендаций) // Терапия. 2019. Т. 5, № 7. С. 9–42. doi: 10.18565/therapy.2019.7.9-42
11. Нечайкина С.А., Мальмберг С.А., Петрухин А.С. Неврологические нарушения при дисплазии соединительной ткани у детей и их коррекция // Русский журнал детской неврологии. 2010. Т. 5, № 3. С. 11–20.
12. Алексеева О.С., Кирик О.В., Гилерович Е.Г., Коржевский Д.Э. Микроглия головного мозга: происхождение, структура и функции // Журнал эволюционной биохимии и физиологии. 2019. Т. 55, № 4. С. 231–241. doi: 10.1134/S0044452919040028
13. Гоголева М.С., Друцкая К.С., Атретханы К.С.-Н. Микроглия в гомеостазе центральной нервной системы и нейровоспалении // Молекулярная биология. 2019. Т. 53, № 5. С. 790–798. doi: 10.1134/S0026898419050057
14. Никифорова (Постникова) Т.А., Песков С.А., Доронина О.Б. Анализ современного состояния клинико-экспериментальных данных о взаимодействии нервной и иммунной систем // Бюллетень сибирской медицины. 2014. Т. 13, № 6. С. 72–80.
15. Zhao M., Tuo H., Wang S., Zhao L. The roles of monocyte and monocyte-derived macrophages in common brain disorders // Biomed Res Int. 2020. Vol. 2020. P. 9396021. doi: 10.1155/2020/9396021
16. Черных Е.Р., Шевела Е.Я., Останин А.А. Роль макрофагов в восстановлении повреждений центральной нервной системы: новые возможности в лечении неврологических расстройств // Медицинская иммунология. 2017. Т. 19, № 1. С. 7–18. doi: 10.15789/1563-0625-2017-1-7-18
17. Сахно Л.В., Шевела Е.Я., Черных Е.Р. Фенотипические и функциональные особенности альтернативно активированнных макрофагов: возможное использование в регенеративной медицине // Иммунология. 2015. Т. 36, № 4. С. 242–246.

AUTHORS' INFO

*** Irina V. Malceva,** assistant lecturer;
address: 40 Lenina avenue, 656038,
Barnaul, Russia;
ORCID: https://orcid.org/0000-0002-4247-2052;
e-mail: ibogd2009@rambler.ru

Irina I. Sheremetieva, MD, Dr. Sci. (Med.), professor;
ORCID: https://orcid.org/0000-0001-8513-9869;
eLibrary SPIN: 8805-6940; e-mail: rector@agmu.ru

Elena F. Kotovshchikova, MD, Dr. Sci. (Med.), professor;
ORCID: https://orcid.org/0000-0002-3246-5609;
eLibrary SPIN: 6358-0981; e-mail: kotov-l@mail.ru

Anastasia A. Selezneva, student;
ORCID: https://orcid.org/0000-0002-1342-1125;
e-mail: selezneva.doc99@mail.ru

Evgenia V. Buylova, MD, Cand. Sci. (Med.), associate professor;
ORCID: https://orcid.org/0000-0002-5647-8105;
e-mail: 693003@list.ru

ОБ АВТОРАХ

*** Мальцева Ирина Владимировна,** ассистент;
адрес: Россия, 656038, Алтайский край,
Барнаул, проспект Ленина, 40;
ORCID: https://orcid.org/0000-0002-4247-2052;
e-mail: ibogd2009@rambler.ru

Шереметьева Ирина Игоревна, д.м.н., профессор;
ORCID: https://orcid.org/0000-0001-8513-9869;
eLibrary SPIN: 8805-6940; e-mail: rector@agmu.ru

Котовщикова Елена Федоровна, д.м.н., профессор;
ORCID: https://orcid.org/0000-0002-3246-5609;
eLibrary SPIN: 6358-0981; e-mail: kotov-l@mail.ru

Селезнева Анастасия Александровна, студентка;
ORCID: https://orcid.org/0000-0002-1342-1125;
e-mail: selezneva.doc99@mail.ru

Буйлова Евгения Викторовна, к.м.н., доцент;
ORCID: https://orcid.org/0000-0002-5647-8105;
e-mail: 693003@list.ru

* Corresponding author / Автор, ответственный за переписку