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LIPID PEROXIDATION, MMP-9 ACTIVITY, AND BDNF LEVEL IN PATIENTS WITH PARANOID SCHIZOPHRENIA DEPENDING ON THE DURATION OF THE DISEASE

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LIPID PEROXIDATION, ACTIVITY OF MATRIX METALLOPROTEINASE-9, AND CIRCULATING LEVELS OF BRAIN-DERIVED NEUROTROPHIC FACTOR DEPENDING ON THE DURATION OF THE DISEASE IN PATIENTS WITH PARANOID SCHIZOPHRENIA

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The research aims to analyze the activity of matrix metalloproteinase-9 indicators (MMP-9), circulating brain-derived neurotrophic factor (BDNF), and malondialdehyde (MDA) levels depending on the duration of the disease in patients with paranoid schizophrenia.

Materials and methods. The research included 320 patients, namely 20 patients with "Primary Psychotic Episode" (Comparison Group) and 300 patients with a diagnosis of "Paranoid Schizophrenia" (Study Group): 60 of them suffered from this disease from 3 to 5 years (Subgroup I); 60 individuals – from 6 to 10 years (Subgroup II); 60 patients – from 11 to 15 (Subgroup III); 60 of them – from 16 to 20 (Subgroup IV); and 60 patients – from 21 years and more (Subgroup V). We assessed the severity of the underlying disease using the Positive and Negative Syndrome Scale. We evaluated the intensity of oxidative stress (OS) by measuring the MDA index. Additionally, we determined the content of MMP-9 and BDNF in the blood serum of all patients using ELISA.

Results. Analysis of the presented results showed that a statistically significant increase in malondialdehyde was observed in all Subgroups, except the first one and indicated an increase in lipid peroxidation processes in patients with schizophrenia for over 5 years. The level of MMP-9 was also significantly increased in patients of the Study Subgroups compared to the Comparison group. Simultaneously, we observed a statistically significant decrease in BDNF values in Subgroups II–V. The degree of BDNF decrease increased with increasing duration of the underlying disease and, therefore, the age of the patients. Thus, the study showed that the levels of MMP-9, BDNF, and MDA might be considered potential biomarkers for assessing the severity and predicting the course of schizophrenia.

Keywords: schizophrenia, oxidative stress (OS), malondialdehyde (MDA), matrix metalloproteinase-9 (MMP-9), brain-derived neurotrophic factor (BDNF).

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ПЕРЕКИСНЕ ОКИСНЕННЯ ЛІПІДІВ, АКТИВНІСТЬ MMP-9 ТА РІВЕНЬ BDNF У ХВОРИХ НА ПАРАНОЇДНУ ШИЗОФРЕНІЮ ЗАЛЕЖНО ВІД ТРИВАЛОСТІ ХВОРОБИ

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Дослідження виявило тісний зв'язок між окисним стресом, запаленням та нейродегенеративними процесами у пацієнтів із шизофренією. Зниження рівня BDNF та підвищення рівнів MMP-9 і MDA свідчать про порушення нейропластичності та посилення запальних процесів, що можуть бути ключовими факторами у розвитку негативної симптоматики. Результати дослідження демонструють, що рівні MMP-9, BDNF та MDA можуть служити потенційними біомаркерами для оцінки тяжкості шизофренії та прогнозування перебігу захворювання. Виявлені кореляції між цими біомаркерами та симптоматикою відкривають нові перспективи для розробки персоніфікованих підходів до лікування.

Ключові слова: шизофренія, оксидативний стрес (ОС), малоновий диальдегід (MDA), матриксна металопротеїназа-9 (MMP-9), нейротрофічний фактор мозку (BDNF).

Introduction

Experimental and clinical studies have found that stress and oxidants predominate among the multiple factors that trigger the pathophysiological cascade of the formation of various diseases in humans [1; 2]. The increased level of the oxidants contributes to the appearance of oxidative stress (OS), in case of which the increased level of free radicals (FR) can attack specific biomolecules causing damage to cells, tissues, and organs. The reason is their nature: FR are oxygen-containing molecules with an odd number of electrons allowing them to respond quickly to other molecules such as DNA, proteins, and lipids. Lipids are a significant component of cell membranes, including neurons. Their oxidation leads to damage to the membranes and impaired cell function. In case of excessive accumulation of oxidation products in the intercellular matrix, a block of normal cell vital processes occurs, and nerve impulses are violated. As a result, all this causes the development of various diseases, including the neurodegenerative ones, such as schizophrenia [3]. Therefore, not only the activity of antioxidant protection enzymes or dynamics of proteins oxidative modification reflected in our previous works but also malondialdehyde (MDA) level, the ratio of oxidants/antioxidants, are the informative indicators for the prediction of the further development of such diseases [4; 5].

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Стаття поширюється на умовах ліцензії

Recent studies have confirmed that the reactive oxygen species (ROS) formed during the OS have an impact on the MMP-9 expression, the growth of which increases the risk of cognitive disorders, schizophrenia in particular [6]. In the central nervous system, MMP-9 is localized and released from neurons, astrocytes, and microglia, and its level of expression is modified by reactive oxygen species formed during OS, cytokine, and growth factors. MMP-9 is a metalloenzyme that breaks down the proteins that form the brain matrix. It is involved in several key neurogenesis processes, including the maturation of inhibitory neurons, the formation of a specialized extracellular matrix structure, synaptic plasticity, and myelinization. However, excessive MMP-9 activity can damage neurons and lead to degradation of healthy brain tissues.

Y. Lu and co-authors report that the expression of matrix metalloproteinases is closely correlated with OS, namely the degree of its manifestation, which determines the relevance of the study of the mutual influence of the prooxidant-antioxidant system state and the expression of matrix metalloproteinases in patients with schizophrenia [7]. According to F. Dickerson and co-authors, people with higher MMP-9 have much higher chances of developing schizophrenia or bipolar disorder [8]. Having examined 39 people with an early phase of psychosis and 44 healthy individuals of the relevant age and gender, Johanna Seitz-Holland and co-authors proved the presence of a relation between MMP-9 activity, microstructural changes in the hippocampus, and cognitive capabilities [9]. It is interesting to note that valproates can reduce MMP-9 levels. Patients receiving medication of this group had much lower MMP-9 levels. It is not yet clear, but it may be due to the ability of valproates to suppress histone deacetylation and have an effect on various immune mediators [10]. A number of studies also indicate that MMP-9 levels increase under LP influence negatively impacting the central nervous system (CNS) [11].

Matrix metalloproteinases (MMP) are calcium-dependent zinc-containing endopeptidases (proteolytic enzymes) that act predominantly extracellularly and regulate the integrity and composition of extracellular matrix (ECM), and MDA "puts together" lipid molecules in the cell and reduces the strength of the membrane, making it fragile [12]. Excessive destruction of ECM under the influence of increased MMP concentration is associated with many physiological and pathological conditions, including schizophrenia. ROS are known to contribute to MMP activation, while antioxidants inhibit the latter's gelatinolic activity and thus protect ECM. In their recent study, which was observational, cross-over, and retrospective by methodology, according to the principle of case-control, H. Yang and co-authors examined 80 male patients with chronic schizophrenia and 80 apparently healthy individuals. The results demonstrated that the levels of superoxididiasmutase (SOD), glutathione peroxidase (GSH-Px) and malone dialdehyde (MDA) were significantly reduced, while catalase (CAT) and MMP-9 levels were increased in patients with schizophrenia compared to healthy individuals in the control group. Correlation analysis conducted in patients with schizophrenia showed that the level of hydrogen peroxide (H_2O_2) substantially and positively correlated with positive PANSS points, CAT and MDA levels significantly correlated with negative PANSS points and the total PANSS points, and MDA levels much more positively correlated with MMP-9 [13].

Brain-derived neurotrophic factor (BDNF) is a protein involved in the nutrition of neurons that helps them grow and create new bonds. It is an indispensable participant in learning because it forms memory. Low BDNF levels are associated with brain plasticity disorders and cognitive problems. Based on the scientific data, MMP-9 can reduce BDNF. Increased MMP-9 activity can probably destroy BDNF receptors reducing its effectiveness. In our research, we want to trace the dynamics of these indicators and the features of their mutual influence, taking into account the duration of the disease in patients with schizophrenia.

The objective of the research is to analyze the activity of matrix metalloproteinase-9, circulation of the brain-derived neurotrophic factor and the level of malone dialdehyde in patients with paranoid schizophrenia, depending on the disease duration.

Materials and methods

The research was performed at the Department of Psychiatry, Narcology and Medical Psychology of Ivano-Frankivsk National Medical University of the Ministry of Health of Ukraine at the premises of the Communal Non-Commercial Enterprise "Prykarpattia Regional Clinical Center for Mental Health of the Ivano-Frankivsk Regional Council" (CNE "PRCCMHIFRC") and the "Pohonia Psychoneurological Residential Care Facility".

Considering the peculiarities of the chosen patients' contingent and the direction of the scientific research, an Experimental Group was formed consisting of five subgroups and a control group. In order to ensure the statistical accuracy of the results and taking into account international practices, we identified the number of individuals for the study groups, namely 60 participants each. For complete gender representation, the proportionality of the participants was considered and achieved (an ideal model included 50% of men and 50% of women). Thus, 320 patients were included in the examination, namely 20 patients with a "primary psychotic episode" (Comparison Group) and 300 individuals with a diagnosis of "paranoid schizophrenia" (Experimental Group): 60 of them suffered from this disease from 3 to 5 years (Subgroup I); 60 individuals – from 6 to 10 years (Subgroup II); 60 patients – from 11 to 15 (Subgroup III); 60 of them – from 16 to 20 (Subgroup IV); and 60 patients – from 21 years and more (Subgroup V).

The severity of the underlying disease was evaluated according to the Positive and Negative Syndrome Scale (PANSS) "Qualification scale of assessment of the severity of positive, negative and general psychopathological syndromes" (Kay S, Opler L, Fiszbein A, 1987).

Studies concerning the condition of the prooxidant-antioxidant system were conducted by means of a photoelectric colorimeter type KFK-2MP № 8903873 of the Center for Microelementology of the Ivano-Frankivsk National Medical University at the Department of Biological and Medical Chemistry named after Academician Babenko GO.

Quantitative determination (concentration) of malone dialdehyde (MDA), which reacts with thiobarbituric acid (TBK) forming a complex of active products (TBK-AP), is widely used in order to estimate the LP intensity.

MMP-9 content in blood plasma in all examined patients was determined by immuno-enzyme analysis by means of Immuno Chem-2100, Microplate Reader, using the laboratory set "The RayBiotech Human MMP-9 Enzyme Immunoassay Kit" (USA) and was expressed in pg/ml.

BDNF indicators in the blood serum of all patients were determined by immuno-enzyme analysis with the use of the set "The Raybiotech Human BDNF Ensyme Immunoassay Kit (USA) were and expressed in PG/ml.

All examinations were conducted only after signing of the informed consent for the examination and treatment under the provision which were approved by the Ivano-Frankivsk National Medical University (Protocol No. 125/23 of 24.05.2023), as well as the Law of Ukraine "On Psychiatric help". During the research, the "Rules of ethical principles of scientific research with human participation", approved by the Helsinki Declaration (1964–2013) were observed and in accordance with the ethical and moral and legal norms. When selecting patients by age, we used the standard age range of 18–65 years for modern research.

The statistical processing of the results was conducted using Statistica 7.0. (Statsoft, Inc.) and the Microsoft Excel, 2016 statistical features. The accuracy of the results was confirmed on the basis of the calculation of the Student's coefficient. We conducted correlation analysis according to Pearson's coefficient. The "–" sign indicated reverse connection, and "+" meant a direct connection. We estimated the force of correlation relationship by the following gradations: r = 0.3 – weak, r = 0.3–0.5 – moderate, r = 0.5–0.7 – significant, r = 0.7–0,9 – strong, r = 0.9–0.99 – very strong. In order to describe quantitative features, we used the median (Me), mode (Mo) and interquartile range: the lower – the higher quartile (LQ-HQ). Arithmetic mean (m), standard error (± m) were used to describe quantitative features.

Results of the research

The difference between the MDA values in the Experimental Subgroups is presented in Figure 1. The average value of this indicator in subgroup I was (3.323 ± 0.054) nmol/ml, which was 0.84% higher than the data in the Comparison Group.

The median of this indicator (Me) in the patients in this group was 3.325; the mode (Mo) constituted 3.19, with an interquartile range (LQ-HQ) – 3.14–3.63 nmol/ml (0.228; P≥0.01) (Fig. 2.). In Subgroup II, the MDA value averaged (3.746 ± 0.102) nmol/ml, which was 13.7% more than in the Comparison Group. In this case, Me amounted 3.72; Mo was 3.65; LQ-HQ – 3.165-4.44 nmol/ml. In Subgroup III, MDA was (4.251 ± 0.082) nmol/ml, which was 29.01% higher than in the Comparison group: Me – 4.365; Mo – 3.79; LQ-HQ – 3.8–4.65. In Subgroup IV, MDA was (4.404 ± 0.064) nmol/ml, which was 33.65% higher than in the Comparison Group: Me – 4.505; Mo – 4.65; LQ-HQ – 4.125–4.69. In Subgroup V, MDA constituted (4.658 ± 0.053), which was 41.36% higher than in the Comparison Group, Me – 4.61, Mo – 4.65; LQ-HQ – 4.345–4.96, respectively.

Figure 3 presents the dynamics of MMP-9 indicators in the examined patients. According to the presented data, the concentration of MMP-9 in the patients of the Comparison group was (971.12 ± 38.26) pg/ml, which was 8.24% less than in the Experimental Subgroup, where this figure constituted (1058.32 ± 53.24) pg/ml. MMP-9 amounted

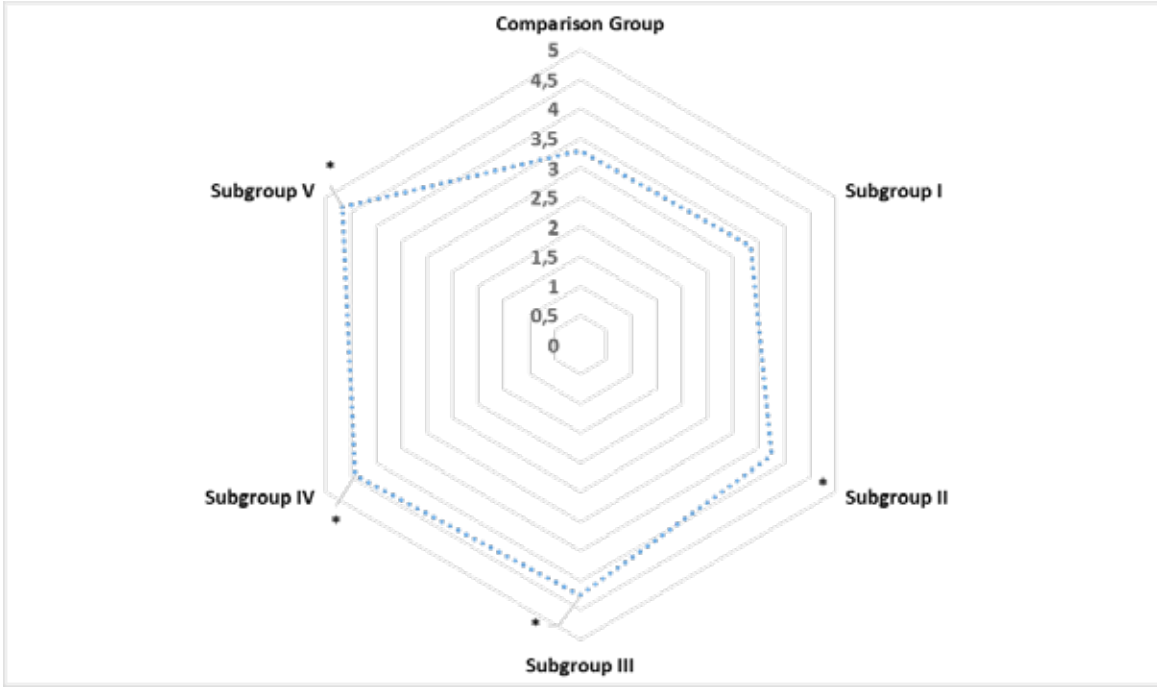

Fig. 1. Dynamics of MDA in the examined groups of patients

Note: * – (P <0.05) The data are reliable compared to the comparison group.

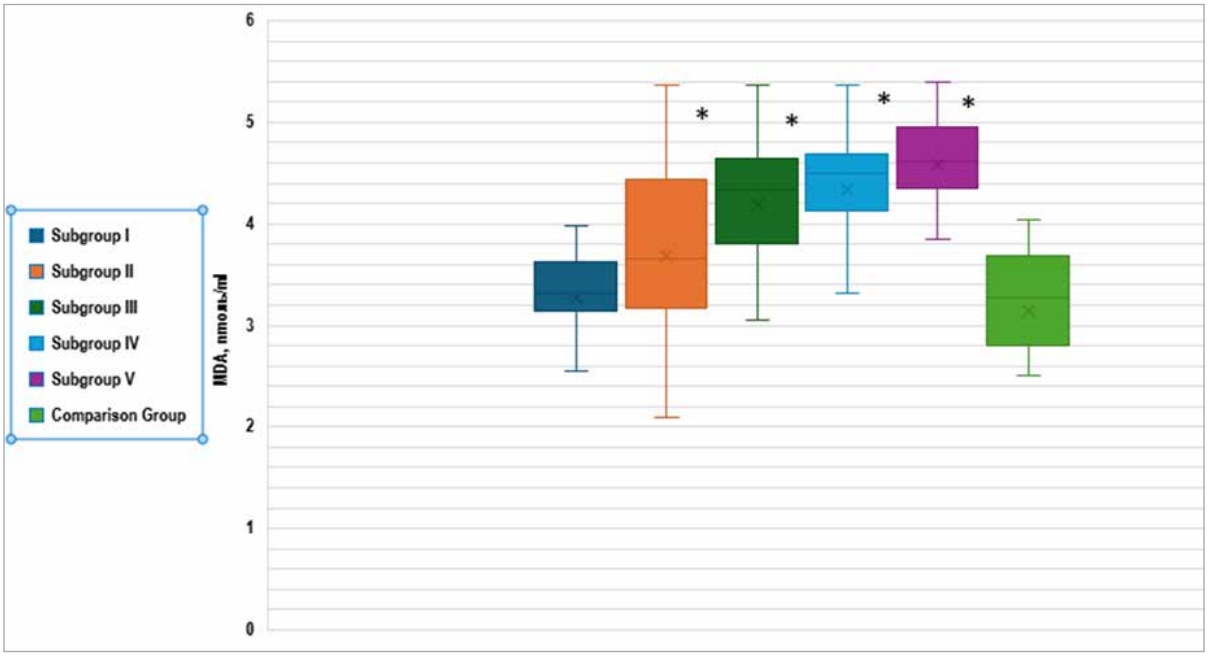

Fig. 2. MDA interquartile range in the groups of examined patients

Note: * – (P <0.05) The data are reliable compared to the comparison group.

(1153.27 ± 67.34) pg/ml in the patients of Subgroup II, which was by 15.79 % higher than in the Comparison group. It was (1831.64 ± 49.37) pg/ml in Subgroup III, being by 46.98% higher than in the Comparison Group. MMP-9 constituted (1761.38 ± 38.29) pg/ml in Subgroup IV, that is by 44.86% higher than in the Comparison Group. This indicator was (2042.84 ± 49.33) pg/ml in Subgroup V, which was almost twice as high as in the Comparison Group (p<0.05).

According to the results of the research, the average BDNF was (27.226 ± 0.165) pg/ml in Subgroup I, which was only 1.7% lower than in the Comparison Group.

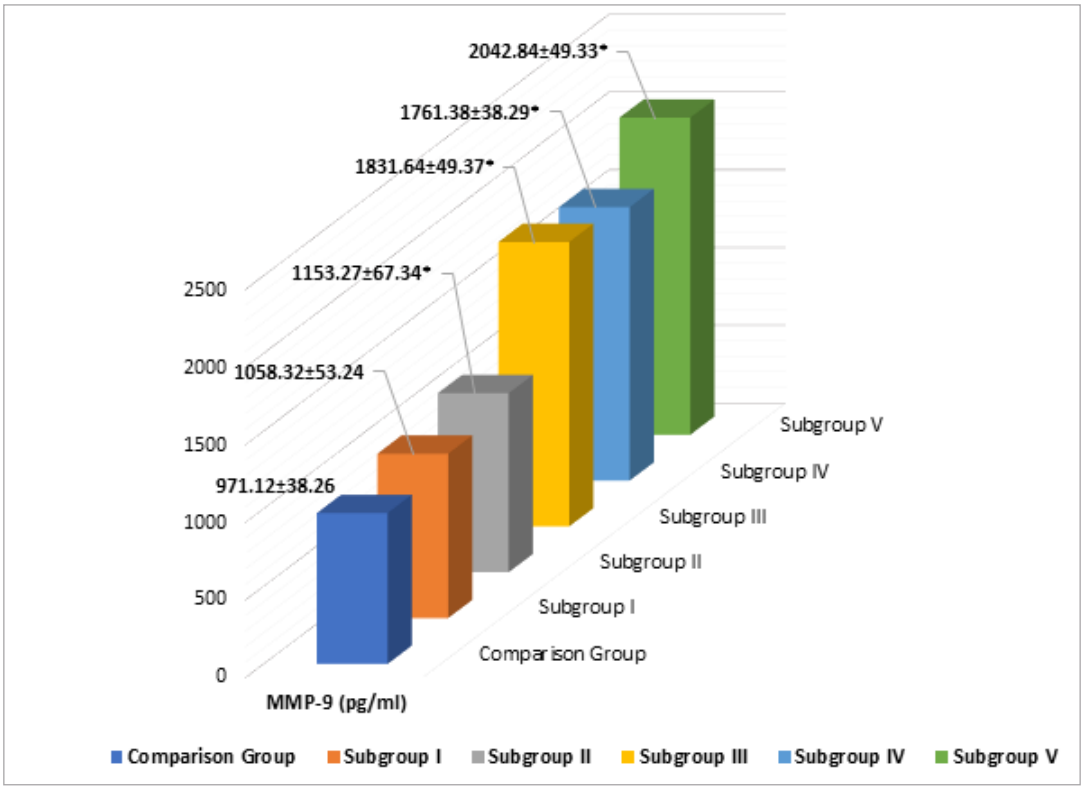

Fig. 3. Dynamics of MMP-9 in the groups of examined patients

Note: * – (p <0.05) The data are reliable compared to the comparison group.

BDNF interquartile ranges in the patients of Subgroup I were 26.17–28.057 pg/ml (Fig. 4). In Subgroup II, this figure constituted (23.787 ± 0.217) pg/ml on average, which was 14.2% lower than in the Comparison Group. BDNF interquartile ranges in the patients of Subgroup II were 22.47–25.082 pg/ml. BDNF amounted (23.754 ± 0.109) pg/ml in Subgroup III, which was 14.3% lower than in the Comparison Group. BDNF interquartile ranges in the patients of Subgroup III were 23.15–24.425 pg/ml. In Subgroup IV, BDNF was (18.345 ± 0.071) pg/ml, being 33.8% lower than in the Comparison Group. BDNF interquartile ranges in the patients of Subgroup IV constituted 17.872–18.662 pg/ml. This figure decreased by more than 2.6 times in Subgroup V, respectively, and was (10.658 ± 0.271) pg/ml. BDNF interquartile ranges in the patients of Subgroup V amounted 9.475–12.477 pg/ml.

The results of correlation analysis (Fig. 5) showed that there was an average inverse correlation between MDA and BDNF. In Subgroup I, the correlation coefficient was -0.463 ($p<0.05$), and the determination ratio (R^2) showed that the variation of the first indicator was determined by the variation of the second one by 21.4%. In Subgroup II, the correlation coefficient was -0.348 ($p<0.05$), and R^2 showed that the variation of the first indicator was determined by the variation of the second one by 12.1 %. In Subgroup III, the correlation coefficient was -0.300 ($p<0.0$), and R^2 showed that the variation of the first indicator was determined by the variation of the second one by 9%. The correlation coefficient was -0.323 ($p<0.05$) in Subgroup IV and R^2 showed that the variation of the first indicator was determined by the variation of the second one by 10.4%. In Subgroup V, the correlation coefficient was -0.499 ($p<0.05$), and R^2 showed that the variation of the first indicator was determined by the variation of the second one by 24.9%. A strong correlation coefficient between MDA and BDNF was detected in the Comparison Group and constituted -0.723 ($p<0.05$), and R^2 showed that the variation of the first indicator was determined by the variation of the second one by 52.0%.

The results of the correlation between the PANSS and BDNF, MMP-9 and MDA indicators are presented in Table 1.

According to the obtained data, we noted a weak negative correlation between the PANSS and BDNF levels, and a weak direct, positive correlation between PANSS and MMP-9 as well as between PANSS and MDA in the Comparison Group. Meanwhile, mainly moderate correlation was observed in Experimental Subgroups. The most significant correlation of BDNF, MMP-9, and MDA was noted in cases of negative psychopathology. In particular, significant correlation was registered between the following indicators: PANSS-N/BDNF – -0.583 ($p<0.05$) in the patients of Subgroup V; PANSS-N/MMP – -9 0.567 and 0.558; ($p<0.05$) in Subgroup IV and Subgroup V, respectively. The data on the relation of positive symptoms to these quantities were also important. A weak negative correlation BDNF and PANSS-P was observed in the patients of the Comparison Group. The correlation was moderate, negative in all Experimental Subgroups. A direct moderate correlation between MMP-9 and PANSS-P was noted in the Subgroups, where schizophrenia had been diagnosed as an underlying disease for more than 10 years. At the same time, MDA/ PANSS-P positively correlated in all Experimental Subgroups, however, the correlation was statistically reliable only in Subgroup V. A statistically significant negative correlation between the PANSS and BDNF, namely -0.396 and -0.455 ($p<0.05$), respectively, was registered only in Subgroups

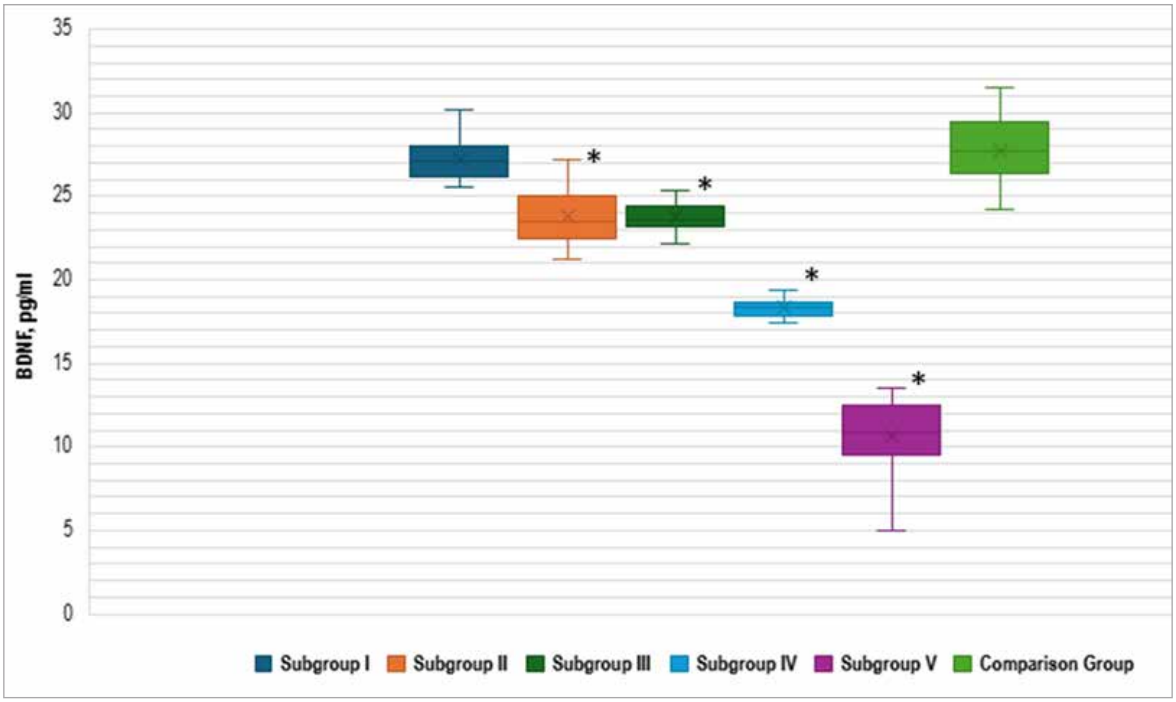

Fig. 4. BDNF interquartile ranges in the examined patients

Note: * – ($P<0.05$) The data are reliable compared to the comparison group.

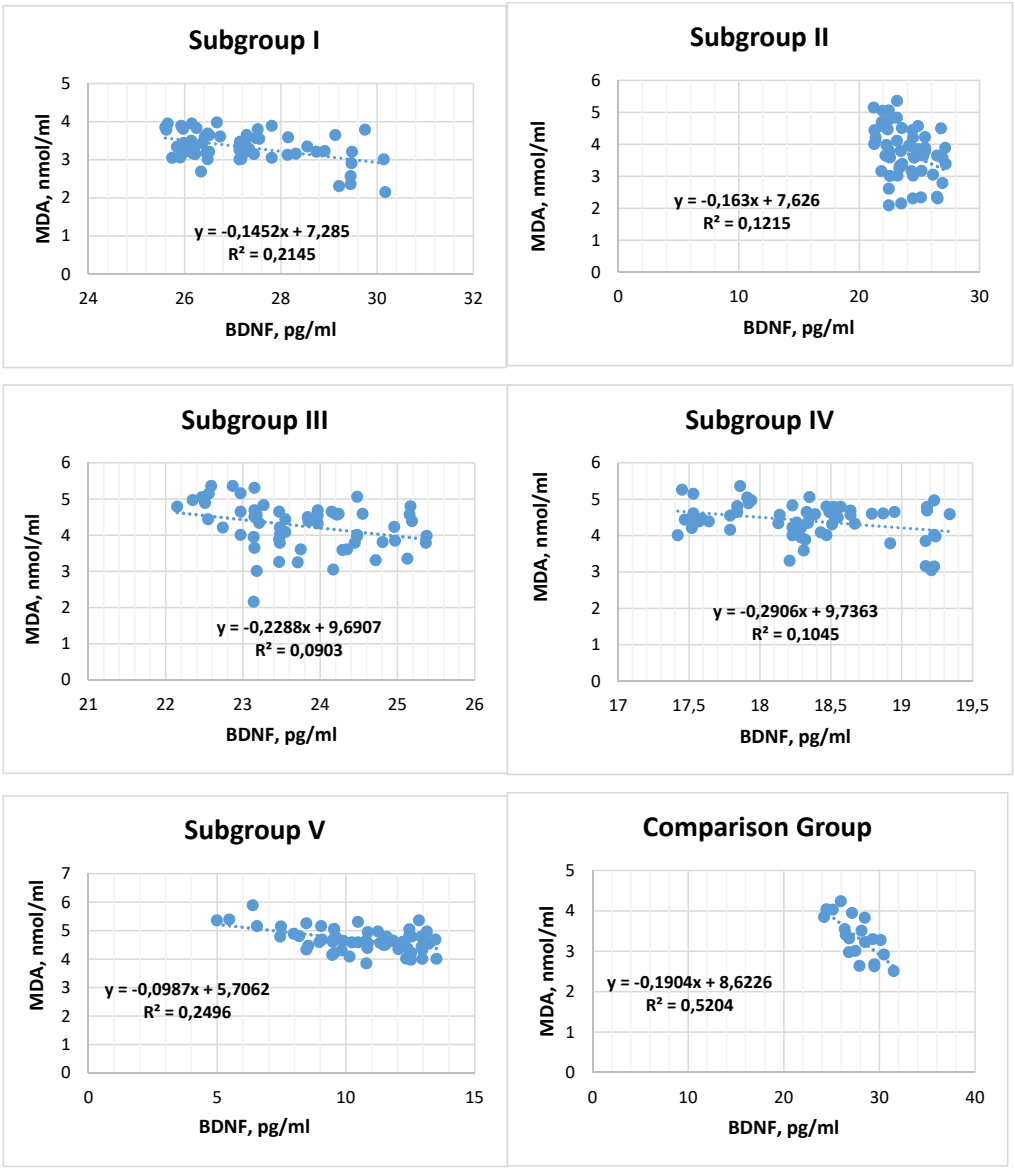

Fig. 5. Correlation between BDNF and MDA in the examined patients

Note: Correlation field and regression line with the equation describing it; R^2 is the coefficient of determination

Table 1

The results of correlation analysis between PANSS and BDNF, MMP-9, MDA in the examined patients

Indicators		PANSS indicators		
		PANSS-N	PANSS-P	PANSS-G (general symptoms)
1	2	3	4	5
BDNF (pg/ml)	The Comparison Group	-0.202*	-0.201*	-0.204*
	Subgroup I	-0.294*	-0.337**	-0.216*
	Subgroup II	-0.238*	-0.354**	-0.278*
	Subgroup III	-0.382**	-0.379**	-0.294*
	Subgroup IV	-0.403**	-0.397*	-0.396**
	Subgroup V	-0.583***	-0.383**	-0.455**
MMP-9 (pg/ml)	The Comparison group	0.284*	0.207*	0.225*
	Subgroup I	0.397**	0.159*	0.295*
	Subgroup II	0.364**	0.287*	0.253*
	Subgroup III	0.389**	0.347**	0.391**
	Subgroup IV	0.567***	0.393**	0.376**
	Subgroup V	0.558***	0.447**	0.389**

Continuation of the table 1

1	2	3	4	5
MDA	The comparison group	0.194*	0.234*	0.213*
	Subgroup I	0.297**	0.299*	0.287*
	Subgroup II	0.308**	0.307**	0.297*
	Subgroup III	0.353**	0.393**	0.491**
	Subgroup IV	0.598***	0.463**	0.406**
	Subgroup V	0.603***	0.557**	0.589***

Notes:

* – weak correlation (P>0.05);

** – moderate correlation (P<0.05);

*** – significant correlation (P<0.05).

IV and V. The MDA correlation was somewhat similar: MDA/PANSS-N statistically significant positive correlation was registered in Subgroups IV and V, namely 0.598 and 0.603 (p<0.05), respectively; MDA/ PANSS-G – Subgroup V – 0.589 (p<0.05).

Discussion

Why are these three components the research subject? A detailed analysis of the scientific literature showed a biological basis, indicating the relationship between these biomarkers. Thus, MMP-9 is involved in the processes of remodeling and pathological processes of neurosis, BDNF takes part in neuromodulation and synaptic plasticity, and MDA is involved in OS [13]. All these processes are closely connected. For example, lipid peroxidation (LP) activates the circulation of MMP-9, thereby contributing to damage to the brain tissues. According to scientific data, MMP-9 is a very important regulator of a crosslink between peripheral and central inflammation, remodeling of extracellular matrix, synaptic contraction and neuroplasticity [14, 15, 16]. Increased MMP-9 activity reduces BDNF and negatively influences neural plasticity. Moreover, under such conditions this neurotrophic factor cannot produce the stimulus necessary for the formation of antioxidants protecting the cell from damage, and thus, a "vicious circle" is formed. Therefore, understanding the relationship between these processes is a lack of a puzzle in the complex mechanism of schizophrenia pathogenesis, the impetus for the development of new regimens for the treatment of neurodegenerative diseases.

According to the analysis of the presented results, a statistically significant increase in MDA levels was observed in all subgroups, except the first one, compared to the comparison group. This indicated an increase in LP in the examined patients with the history of the disease for over 5 years. The most significant increase in MDA was observed in the subgroups with the longest duration of the underlying disease. This indicated the fact that a prolonged paranoid schizophrenia might lead to increased oxidative stress. The obtained data are comparable with the results of the work of H. Yang and co-authors [13]. Since LP intensification is associated with the development of many diseases, such as diabetes, atherosclerosis, and various neurodegenerative diseases, the increased MDA levels might be an additional risk factor for the development of these comorbid conditions.

The results indicated that the MMP-9 level was significantly increased in the patients of the study groups compared to the comparison group. This can indicate the activation of inflammation, tissue damage, and, therefore, the progression of the disease. The results indicated the important role of MMP-9 in the pathogenesis of the disease, as well as that it may be a marker of the disease activity and predict its course.

Thus, the research showed a decrease in BDNF in all subgroups. A statistically significant decrease in BDNF was observed in Subgroups II-V compared to the Comparison group. This indicated a general tendency to the deficiency of this neurotrophic factor in the studied sample. The most significant decrease was observed in Subgroup V, where BDNF level was almost 2.6 times lower than in the Comparison Group. The degree of BDNF decrease increases with the increase in the duration of the underlying disease and, therefore, the age of patients.The interquartile range showed that not only did the average value of BDNF decrease, but the variation of values in all Subgroups decreased as well indicating a more homogeneous decrease in the level of this protein. Decreased BDNF may be associated with neuronal death processes characteristic of many neurodegenerative diseases, including schizophrenia. Chronic inflammation can also have a negative impact on BDNF levels.

The correlation analysis results indicated a reverse connection between MDA levels as an oxidative stress marker and BDNF. That is, BDNF level usually decreased with an increase in MDA level. Such data support the hypothesis that OS has a negative effect on neuroplasticity by reducing BDNF levels. According to scientific data, the probable ways of this connection are violation of BDNF gene expression under the OS influence, changes in the activity of its receptors, or direct damage to its molecules with free radicals.

The results of correlation analysis indicated complex relationships between psychopathological symptoms assessed by the PANSS and BDNF, MMP-9 and MDA biomarkers. There was a clear negative correlation between negative symptoms and BDNF levels. It was predominantly expressed in the patients with a longer course of the disease. It may have resulted from a violation of neuroplasticity in some brain regions. A positive correlation between the level of negative symptoms and MMP-9 and MDA indicators was observed indicating the presence of chronic inflammation and OS. These data partially contradicted the results of H. Yang and co-authors, who had found that MDA levels significantly negatively correlated with PANSS-P and

PANSS-G, and no correlation was found between MMP-9 and the total score of the PANSS or its subscales. It should be noted that only men participated in that study, and our research involved the participation of both genders in equal proportions [13]. The obtained data indicated a complex interaction of various biological processes, such as neuroplasticity, inflammation, and OS [16].

Therefore, the conducted research showed that MMP-9, BDNF, and MDA levels might be considered as potential biomarkers for assessing the severity of schizophrenia and predicting its course. Therefore, the biological approach of this study provides new prospects for developing an individual approach to the treatment of this pathology aimed at modulating stress, inflammation, and synaptic plasticity.

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