ORIGINAL ARTICLE

PECULIARITIES OF BRAIN-DERIVED NEUROTROPHIC FACTOR AND MATRIX METALLOPROTEINASE-9 EXPRESSION DYNAMICS IN PATIENTS WITH PARANOID SCHIZOPHRENIA DEPENDING ON THE DURATION OF THE DISEASE

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ABSTRACT

The aim: To study the expression of brain-derived neurotrophic factor (BDNF) and matrix metalloproteinase-9 (MMP-9) in the blood serum of patients with paranoid schizophrenia and to trace the features of their dynamics depending on the duration of the disease and analyse the correlation between BDNF, MMP-9 serum levels and symptoms severity by using the Positive and Negative Syndrome Scale (PANSS).

Materials and methods: The study included 120 patients, namely 20 patients with paranoid schizophrenia diagnosed less than 3 years ago (Comparison Group) and 100 patients with a diagnosis of paranoid schizophrenia (Study Group): 20 of them have been suffering from this disease from 3 to 5 years (Subgroup I); 10 patients – from 5 to 10 years (Subgroup II); 10 patients – from 10 to 15 years (Subgroup III); 10 patients – from 15 to 20 years (Subgroup IV); 10 patients – from 25 years and more (Subgroup V). The groups did not differ with respect to age or gender. The content of BDNF and MMP-9 in blood serum was determined by enzyme-linked immunosorbent assay.

Results: BDNF concentration averaged 28.327 ± 5.32 pg/ml in the patients of Group I; 25.40 ± 2.31 pg/ml in Group II; 24.32 ± 3.1 pg/ml in Group III; 23.8 ± 1.32 pg/ml in Group IV; 21.39 ± 0.97 pg/ml in Group V; 9.36 ± 4.38 pg/ml in Group VI. The expression of MMP-9 in the experimental groups constituted: 942.84 ± 87.80 pg/ml, 1042.84 ± 87.80 pg/ml, 1142.53 ± 77.20 pg/ml, 1752.84 ± 77.80 pg/ml, 1542.84 ± 37.70 pg/ml, 2042.74 ± 47.80 pg/ml, respectively. Decreased BDNF negatively correlated with MMP-9 expression ($r=0.46$; $p<0.05$).

Conclusions: The development of paranoid schizophrenia was manifested by an imbalance in BDNF level and MMP-9 expression which could affect neurogenesis, synaptic plasticity, ability to learn and remember, therefore, they could be considered as diagnostic markers of the pathology. With the increase in the duration of the studied pathology, BDNF parameters decreased and MMP-9 expression increased. A negative correlation between them was noted.

KEY WORDS: paranoid schizophrenia, brain derived neurotrophic factor, matrix metalloproteinase-9, neuroplasticity

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INTRODUCTION

The prevalence of schizophrenia in the population is estimated at approximately 0.7-1.0%. According to the Global Burden of Disease Study (GBD) 2017, schizophrenia is one of the most disabling and costly disorders [1-3].

In an attempt to find a neurobiological explanation for schizophrenia, a "disconnection hypothesis" has been offered. According to this hypothesis, the pathogenetic core of schizophrenia is a violation of functional connections between neural networks. According to the scientific data, the disconnection is caused by the dysfunction of N-methyl-d-aspartate receptors (NMDAR) and disorders of modulation of synaptic plasticity which provides the ability to change the sensitivity of the synapse in response to activation of postsynaptic receptors [4]. The involvement of these phenomena in the pathophysiology of schizophrenia has been studied in recent years. The NMDAR hypofunction hypothesis has been proposed to help understand the etiology and pathophysiology of schizophrenia. This hypothesis is based on early observations that NMDAR antagonists can cause the full range of schizophrenia symptoms in normal people. In particular, scientists and clinicians have noticed that if healthy volunteers are administered drugs that are blockers of NMDA receptors (a significant part of them are used for anesthesia), they can contribute to very similar symptoms as in case of schizophrenia, namely delusions, hallucinations, paranoia, disorganization of thinking and speech, etc. [5, 6].

In recent years, the concept of neuroplasticity has been formulated. It lies an extraordinary property of nervous tissue to structural and functional rearrangement and restoration of lost neural connections in case of damage [4]. Neurotrophic factors, a group of endogenous polypeptides play an important role in the regulation of neuroplasticity processes. The leading mediator in the mechanisms of neurogenesis and neuroplasticity is considered to be the brain derived neurotrophic factor (BDNF). It is one of the physiologically active polypeptides that regulate the growth and differentiation of neurons in the process of phylogenesis promoting the formation of new synaptic

connections [7]. As the main mechanism for memory and learning, synaptic plasticity plays an important role in the pathogenesis of schizophrenia, and matrix metalloproteinase-9 (MMP-9) is able to disrupt this synaptic plasticity. According to the scientific data, MMP-9 plays an important role in BDNF maturation on the way to its transformation from proBDNF to biologically active mature BDNF. In addition, in stimulated neurons, the matrix MMP-9 is secreted from dendritic spines, in which short single or multiple protrusions of the postsynaptic membrane of the dendrites come into contact with synaptic expansion. Spiny devices significantly increase the number of synaptic contacts on the neuron, and hence the amount of processed information [8].

According to epy scientific data, BDNF plays an important role in the pathogenesis of the paranoid form of schizophrenia. It is able to stimulate the growth of neurons, axons and dendrites, participates in the formation of synapses and other processes of neuroplasticity. According to the recent scientific data, this property is present not only in early ontogenesis, but also in the brain of an adult, which was previously considered impossible. Decreased serum levels correlate with the severity and duration of the disease and affect the effectiveness of treatment. We also have more and more research on the effects of the BDNF gene on the development and manifestations of schizophrenia as a disease in general [9, 10].

BDNF is also closely related to the serotonergic (5-HT) system of the brain, which is actively involved in various behaviors, including aggression regulation, plays an important role in learning processes, namely memory consolidation, sleep regulation, sexual motivation. According to the latest scientific data, BDNF has a protective effect on damage to 5-HT neurons, increasing the number of their axons. Popova NK and co-authors, reviewing the literature and comparing the information with their own research confirmed the positive effect of BDNF on the 5-HT system of the brain, even a month and a half after a single central injection of its synthetic analogue. This unique feature of its action further confirms its exceptional role in the formation of synaptic connections and in neurogenesis [11].

Therefore, as can be seen from the literature analysis, at present, there are limited scientific data on the relationship between BDNF and MMP-9 in case of schizophrenia, and their dynamics depending on the duration of this pathology has not been studied, which determines the relevance of this study [12].

It is apparent that the indicators of BDNF and MMP-9 in the blood serum will be characterized by fluctuations depending on the duration of the disease. Tracing the patterns of the fluctuations will provide a possibility to predict and conduct therapy for this category of patients more rationally.

THE AIM

The aim was to study the expression of brain derived neurotrophic factor (BDNF) and matrix metalloproteinase-9 (MMP-9) in the blood serum of patients with paranoid schizophrenia and to trace the features of their dynamics depending on the duration of the disease and to analyse the correlation between BDNF, MMP-9 serum levels and the symptoms severity by using the Positive and Negative Syndrome Scale (PANSS).

MATERIALS AND METHODS

The research was conducted at the premises of the Municipal non-commercial enterprise «Precarpathian regional clinical center of mental health of Ivano-Frankivsk regional council» and «Pohonyansky psychoneurological residential care facility». The diagnosis was verified according to the criteria of ICD-10 (F20.0).

The study included 120 patients. The patients were divided into two groups. Group I (Comparison Group) consisted of 20 patients with Paranoid schizophrenia diagnosed less than 3 years ago and Group II (Study Group) included 100 patients with a diagnosis "Paranoid schizophrenia" diagnosed more than 3 years ago: 20 of them have been suffering from this disease from 3 to 5 years (Subgroup I); 10 patients – from 5 to 10 years (Subgroup II); 10 patients – from 10 to 15 years (Subgroup III); 10 patients – from 15 to 20 years (Subgroup IV); 10 patients – from 25 years and more (Subgroup V). The groups did not differ with respect to age or gender.

The main criteria for inclusion in the study groups were as follows: the presence of "Paranoid schizophrenia" diagnosis, individual consent of the patient.

Symptoms of schizophrenia were assessed using the Positive and Negative Syndrome Scale (PANSS). Cases of schizophrenia with the comorbidities of substance-related disorders or mental retardation were excluded.

The concentration of MMP-9 was determined in all subjects by enzyme-linked immunosorbent assay on the device "Immuno Chem-2100, Microplate Reader", using the laboratory kit "The RayBiotech Human MMP-9 Ensyme Immunoassay Kit" (USA) and expressed in pg/ml.

BDNF indices were determined in all patients in the blood serum by enzyme immunoassay method with the use of RayBio® Human BDNF Ensyme Immunoassay Kit (RayBiotech, Inc. USA).

To minimize assay variance, plasma levels of mature BDNF and MMP-9 were measured in each patient on the same day.

The research was approved by the Bioethics Committee of the Ivano-Frankivsk National Medical University and conducted according to the principles of the Helsinki Declaration. All patients signed a voluntary informed consent before the study.

Statistical processing and visualization of the obtained results was performed using the statistical package of the Microsoft Excel 2016 program. The significance of the obtained results was confirmed on the basis of the calculation of Student's coefficient. Correlation analysis was conducted according to Pearson correlation coefficient. The quantitative characteristics were described using arithmetic mean (M), standard error (± m), mode (Mo), median (Me).

Table I. The results of the correlation analysis between the indicators of the PANSS scale and the indicators of BDNF and MMP-9 in the examined patients

Indices		PANSS scale indicators		
		PANSS-N	PANSS-P	PANSS (general symptoms)
BDNF (pg/ml)	Comparison Group	-0.172*	-0.151*	-0.144*
	Subgroup I	-0.252*	-0.365**	-0.196*
	Subgroup II	-0.215*	-0.362**	-0.298*
	Subgroup III	-0.362**	-0.396**	-0.234*
	Subgroup IV	-0.393**	-0.316*	-0.365**
	Subgroup V	-0.521***	-0.363**	-0.431**
MMP-9 (pg/ml)	Comparison Group	0.263*	0.135*	0.195*
	Subgroup I	0.382**	0.130*	0.225*
	Subgroup II	0.321**	0.281*	0.237*
	Subgroup III	0.352**	0.315**	0.361**
	Subgroup IV	0.534***	0.372**	0.397**
	Subgroup V	0.531***	0.434**	0.312**

Notes:
* – weak correlation (p>0.05);
** – moderate correlation (p<0.05);
*** – significant correlation (p<0.05).

Table II. The results of the correlation analysis between the indicators of BDNF and MMP-9 in the examined patients

Indices		BDNF (pg/ml)	
		r	p
MMP-9 (pg/ml)	Comparison Group	-0,234	>0.05
	Subgroup I	-0.454	<0.05
	Subgroup II	-0.397	<0.05
	Subgroup III	-0.413	<0.05
	Subgroup IV	-0.361	<0.05
	Subgroup V	-0.431	<0.05

RESULTS AND DISCUSSION

The relationship between BDNF levels and the severity of psychopathology was studied in the course of the research. The results of the correlation between the PANSS scale and the level of BDNF and MMP-9 are shown in Table I.

According to the obtained data, a weak negative relation between the data of the PANSS scale and the BDNF level was noted in the Comparison Group, as well as a direct, positive connection and between PANSS and MMP-9. Whereas mainly moderate correlation was observed in the experimental subgroups. The most significant negative correlation between BDNF and MMP-9 was observed with the manifestations of negative psychopathology. In particular, astrong correlation was recorded between: PANSS-N / BDNF -0.521 (p<0.05) in Subgroup V patients; PANSS-N / MMP-9 0.534 and 0.531; (p<0.05) in Subgroup IV and Subgroup V, respectively. The data on the relation of positive symptoms with these values were equally important. A weak negative correlation between the BDNF and PANSS-P was noted in the patients of the Comparison Group. That correlation was moderate and negative in all research subgroups. Statistically significant negative correlations were registered between the indicators of general symptoms according to the PANSS scale and BDNF only in subgroups IV and V, constituting -0.365 and -0.431 (p<0.05), respectively. The results of the study of MMP-9 level in the serum of the examined patients are shown in Figure 1.

As can be seen from the data presented, the concentration of MMP-9 in the patients of the Comparison Group constituted 942.84 ± 87.80 pg/ml, which was 9.38% less compared to the first experimental subgroup, where this figure constituted 1042.84 ± 87.80 pg/ml.

MMP-9 constituted 1142.53 ± 77.20 pg/ml on average in the patients of Subgroup II, which was by 21.21% more than in the Comparison group. It constituted 1752.84 ± 77.80 pg/ml in the Subgroup III, which was by 85.9% higher compared to the Comparison group. MMP-9 constituted 1542.84 ± 37.70 pg/ml in the Subgroup IV, which was by 63.6% higher than in the Comparison group. It amounted to 2042.74 ± 47.80 pg/ml in the Subgroup IV,

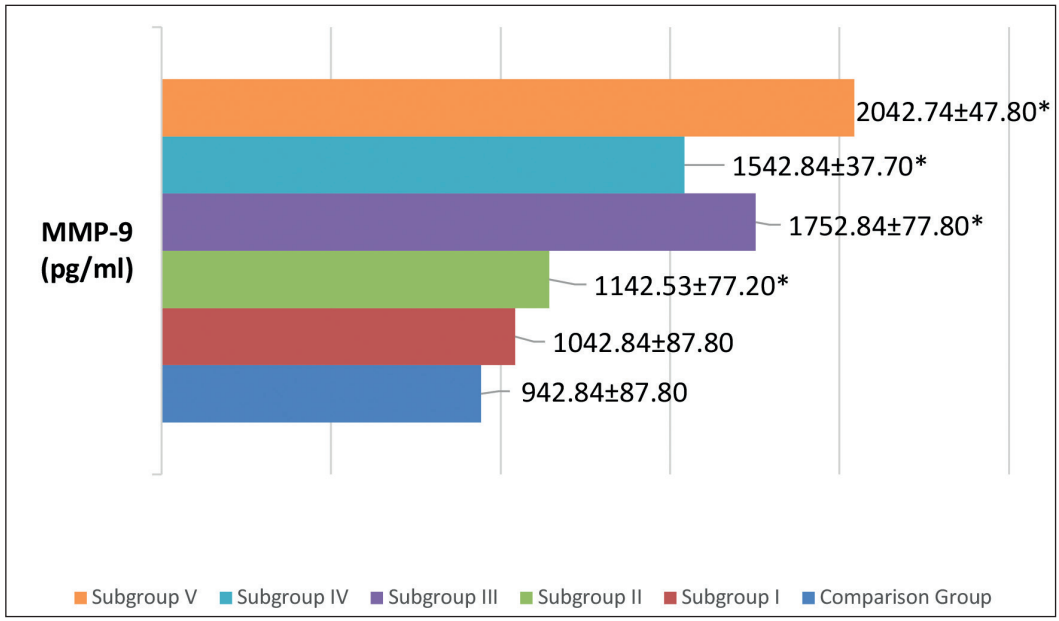

Fig. 1. MMP-9 level in the serum of the examined patients Note: * – ($p<0.05$) the data are reliable between the comparison and study subgroups.

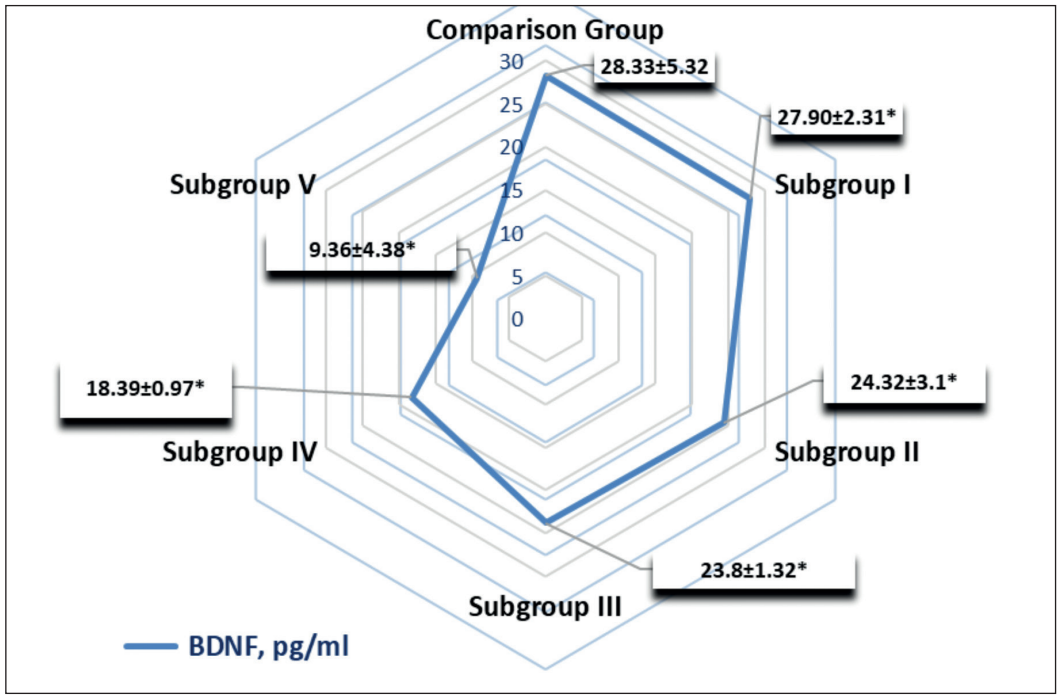

Fig. 2. BDNF level in the serum of the examined patients Note: * – ($p<0.05$) the data are reliable between the comparison and study subgroups.

which was more than twice as high as in the Comparison group ($p<0.05$).

As can be seen from the data presented in Figure 2, BDNF concentration in the patients of the Comparison group averaged 28.327 ± 5.32 pg/ml, while these values were slightly lower in the main Experimental groups. In particular, this indicator was lower by only 1.4% in Subgroup I as well as in the Comparison Group and amounted to 27.90 ± 2.31 pg/ml. It was lower by 14.12% and constituted 24.32 ± 3.1 pg/ml in the Subgroup II. This indicator was lower by 15.96% and amounted to 23.8 ± 1.32 pg/ml in the Subgroup III. It decreased by 35.06% and constituted 18.39 ± 0.97 pg/ml in the Subgroup IV., the value of BDNF was lower than in the Comparison group by as much as 66.9% in the Subgroup V and amounted to 9.36 ± 4.38 pg/ml ($p<0.05$).

Thus, it should be noted that this figure is inversely proportional to the duration of the disease, and its sharp decline occurs after 5 years of illness. Our data partially coincide with the studies of Yamamori H et al. [8].

The results of the correlation analysis are shown in Table II. According to the presented data, a significant inverse moderate correlation between MMP-9 and BDNF was observed in the patients of all experimental subgroups. Whereas a weak inverse correlation was noted in the Comparison Group. A similar tendency was observed by Hen-

driati D and co-authors [13]. Thus, the decrease in BDNF in the patients with paranoid schizophrenia was negatively correlated with MMP-9 expression, and the strength of this relationship increased with increasing duration of the disease. The obtained data confirmed that MMP-9 played a special role in the maturation of BDNF by converting it from proBDNF to biologically active mature BDNF.

CONCLUSIONS

Paranoid schizophrenia was established to be manifested by an imbalance in BDNF levels and MMP-9 expression being able to affect the processes of neurogenesis, synaptic plasticity. According to the PANNS scale, this affected emotions, thought processes, cognition, caused loss of interest in social and environmental phenomena, contributed to memory impairment, therefore, they could be considered as diagnostic markers of such pathology. With the increase in the duration of the studied pathology, BDNF parameters decreased and MMP-9 expression increased. A negative correlation between them was noted. Therefore, the approach to such patients' treatment should take into account these changes.

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The Authors declare no conflict of interest.

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