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Assessment of serum BDNF levels in complex rehabilitation of patients with ischemic stroke using traditional approaches to the restoration of motor functions

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ABSTRACT

Aim. To assess the relationship between changes in serum brain-derived neurotrophic factor (BDNF) level, regression of motor deficiency, and restoration of functional activity in patients with ischemic stroke after stage II of medical rehabilitation.

Materials and methods. The study included 49 patients with ischemic stroke in the middle cerebral artery after stage I of medical rehabilitation. Group I (n = 32) went through stage II of rehabilitation in the early recovery period, group II (n = 17) was discharged for outpatient monitoring at the place of residence. Observation points: day 14 and day 90. Evaluation scales: National Institute of Health Stroke Scale (NIHSS), Fugle – Meyer Scale (FMA), Modified Rankin Scale (mRS). Serum BDNF levels were determined using a MAGPIX multiplex analyzer (Luminex, USA).

Results. A comparative analysis of the studied population showed that patients who underwent motor rehabilitation in the early recovery period had greater regression of neurologic deficit according to the ΔNIHSS scale ($p_{gr.I–II}$ = 0.043), a more pronounced increase in the functional activity on the ΔmRS scale ($p_{gr.I–II}$ = 0.047), and positive dynamics according to the FMA scale ($p_{day14–90}$ = 0.003) in comparison with patients who received outpatient follow-up. The concentration of BDNF was significantly reduced by the end of the early recovery in the group II ($p_{day14–90\_gr.II}$ = 0.002). On the contrary, there was no decrease in the level of the BDNF ($p_{day14–90\_gr.I}$ = 0.613) in the group of patients undergoing rehabilitation.

Conclusion. The results of the study demonstrated the clinical effectiveness of stage II of the comprehensive rehabilitation of patients in the early period of stroke recovery. We can suggest that the success of neurorehabilitation is closely associated with an increase of the BDNF level against the background of its performance. This makes BDNF a potential marker of evaluating the effectiveness of ongoing rehabilitation treatment

Key words: ischemic stroke, brain-derived neurotropic factor, rehabilitation, early recovery period, neuroplasticity.

Conflict of interest. The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.

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Conformity with the principles of ethics. All the participants of the study signed an informed consent. The study was approved by the local Ethics Committee at Siberian State Medical University (Protocol No. 114 of 22.10.2018).

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Оценка уровня сывороточного BDNF при комплексной реабилитации пациентов с ишемическим инсультом с использованием традиционных подходов к восстановлению моторных функций

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РЕЗЮМЕ

Цель – оценить взаимосвязь между изменением уровня сывороточного BDNF, регрессом моторного дефицита и восстановлением функциональной активности у пациентов с ишемическим инсультом после II этапа медицинской реабилитации.

Материалы и методы. В исследовании приняли участие 49 пациентов с ишемическим инсультом в бассейне средней мозговой артерии после I этапа медицинской реабилитации. Группа I (n = 32) прошла II этап реабилитации в ранний восстановительный период, группа II (n = 17) выписана на амбулаторное наблюдение по месту жительства. Точки наблюдения: 14-е и 90-е сут. Оценочные шкалы: шкала инсульта Национального института здоровья (NIHSS), шкала Фугл – Мейера (FMA), модифицированная шкала Рэнкина (mRS). Уровень BDNF в сыворотке крови определяли на мультиплексном анализаторе MAGPIX (Luminex, США).

Результаты. Сравнительный анализ исследуемой популяции показал, что пациенты, получавшие моторную реабилитацию в раннем восстановительном периоде, имеют бóльший регресс неврологического дефицита по шкале ΔNIHSS ($p_{гр.I–II} = 0,043$), более выраженное повышение **функциональной активности** по шкале ΔmRS ($p_{грI.–II} = 0,047$) и положительную динамику по шкале FMA ($p_{сут14–90} = 0,003$) в сравнении с пациентами, находившимися на амбулаторном наблюдении. Концентрация BDNF значимо снижалась к концу раннего восстановительного периода у пациентов на амбулаторном наблюдении в группе II ($p_{сут14–90\_гр.II} = 0,002$). В группе пациентов, проходивших реабилитацию, напротив, снижения уровня фактора не наблюдалось ($p_{сут14–90\_гр.I} = 0,613$).

Заключение. Результаты исследования демонстрируют клиническую эффективность II этапа комплексной реабилитации пациентов в ранний восстановительный период инсульта и дают основание предположить, что успех нейрореабилитации тесно связан с повышением BDNF на фоне ее проведения. Это делает мозговой нейротрофический фактор потенциальным маркером оценки эффективности проводимого восстановительного лечения.

Ключевые слова: ишемический инсульт, мозговой нейротрофический фактор, реабилитация, ранний восстановительный период, нейропластичность.

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INTRODUCTION

Ischemic stroke is a significant medical and social problem all over the world [1]. More than 50% of patients who have had an ischemic stroke are unable to return to a full life due to the persistence of a disabling neurologic deficit, which in most cases is caused by motor impairment [2]. In this regard, successful rehabilitation of stroke patients is one of the most essential problems of modern medicine [3].

The effectiveness of motor rehabilitation is closely related to the mechanisms of neuroplasticity – the ability of brain neurons to functionally and structurally reorganize themselves [4, 5]. Currently, the role of the brain-derived neurotrophic factor (BDNF) in neurogenesis, plasticity, and neuronal survival induced by damage to brain tissue under conditions of cerebral ischemia is actively studied. BDNF is one of the most studied proteins of the neurotrophin family, which promotes survival, growth, and differentiation of cells in the cerebral cortex and hippocampus [5–9]. In addition, BDNF is involved in the processes underlying cellular mechanisms of memory and motor learning [10–12].

There are two pathways for BDNF expression in the central nervous system. The first is an unregulated constitutive pathway – ischemic stroke induces synthesis of BDNF and expression of its receptors [13]. The second – a dependent pathway – the expression of BDNF increases during motor learning as a result of movement repetition, under the influence of sensory stimulation and activation of the primary motor cortex. The activity-dependent release of BDNF plays a key role in synaptic plasticity in motor rehabilitation [5, 14, 15].

Most of the studies on investigating the relationship between the BDNF levels and post-stroke exercise have been conducted in animals. A number of experimental studies have shown that different intensity and effectiveness of physical activity have different effects on the level of BDNF [16]. Too high intensity and high frequency of physical activity can have a negative therapeutic effect after stroke and slow down motor recovery [17]. The type of exercise also affects the concentration of BDNF. The results of most experimental studies demonstrate an increase in the level of BDNF against the background of aerobic exercise, at the same time, the data on the effect of anaerobic functional training sessions on the level of BDNF are contradictory [18].

In view of insufficient data on changes in the BDNF concentration during rehabilitation after ischemic stroke, obtained as a result of clinical trials, the study of the dynamics of changes in the level of neurotrophin depending on the type, intensity, and frequency of motor training and assessment of its effect on the outcome of stroke are relevant. Solving these problems will answer the questions if is it possible to use BDNF to predict the outcome of ischemic stroke and assess the effectiveness of rehabilitation methods, as well as the use of which types of neurorehabilitation is the most rational.

The aim of the study was to assess the relationship between changes in serum BDNF level, regression of motor deficiency, and restoration of functional activity in patients with ischemic stroke after stage II of medical rehabilitation.

MATERIALS AND METHODS

A prospective, non-randomized, comparative parallel study was conducted from March 2018 to December 2019. The study included patients over 18 years of age who signed a voluntary informed consent (or a consent was obtained from close relatives). The diagnosis of ischemic stroke was confirmed by CT or MRI of the brain. Exclusion criteria were other lesions of the central and peripheral nervous system; HIV, syphilis, viral hepatitis; oncological diseases; transient ischemic attack, hemorrhagic or recurrent ischemic stroke.

The study was approved by the local Ethics Committee at Siberian State Medical University (Protocol No. 114 of 22.10.2018).

For each study participant, a life history was collected, neurological status was assessed, and venous blood was taken to determine the level of serum BDNF. Traditional approaches to the restoration of motor functions at the stage II of medical rehabilitation at the Branch of Research Institute of Balneology and Physiotherapy of the Siberian Federal Scientific Clinical Center of Federal Medicobiological Agency include local air cryotherapy applied to the area of spastic muscles, functional electrical stimulation, stimulation of antagonist muscles to spastic muscles, manual classical massage of paretic limbs, and exercise therapy (therapeutic physical gymnastics on the Bobath treatment table, active gymnastics, walking on a treadmill, walking in rehabilitation bars and stairs with an adjustable step height).

Specialists of the multidisciplinary rehabilitation team selected adequate physical activity for the patient, drawing up a plan for their adequate mobilization and rehabilitation, depending on the results of low-load functional tests, assessment of a patient's likelihood of falling on the Morse Fall Scale, post-stroke spasticity patterns, measurement of peripheral muscle strength on the Medical Research Council (MRC) scale, assessment of spasticity in different muscle groups on the Ashworth Scale, and evaluation of violation of the hierarchical control over the motor function by the nervous system. The duration of one training session was 30 minutes, the frequency of sessions was 2 times a day with a break of at least 2 hours, the course consisted of 20 workouts. The functional state of the patient during the rehabilitation measures was controlled by the heart rate, blood pressure level, and oxygen saturation in the blood. The observation period was early recovery period (90 days from the onset of stroke). Rating scales included National Institutes of Health Stroke Scale (NIHSS), Fugl – Meyer Assessment (FMA), and Modified Rankin Scale (mRS) [19]. The BDNF level in the blood serum was determined on a MAGPIX multiplex analyzer (Luminex, USA) using an HND-G3MAG-36K panel manufactured by MILLIPLEX® MAP (Merck, Germany). The results obtained were expressed in pg / ml.

Statistical processing of the results was carried out using the Statistica 13.0 software package. The critical level of significance when testing statistical hypotheses was taken equal to 0.05 (p is the achieved level of significance). Categorical parameters were described in the form of absolute and relative (%) frequencies of occurrence, quantitative and ordinal ones – in the form of the median and the interquantile range Me (Q_1; Q_3). Comparison of two independent samples was performed using the Mann – Whitney test. To analyze the differences in parameters between the three groups, the nonparametric Kruskal – Wallis test was used, followed by pairwise comparison using the Bonferroni correction for multiple comparisons when the differences were detected. To compare qualitative parameters between the groups, the Pearson's chi-squared test was used. In order to assess the intragroup dynamics of parameters, the Wilcoxon test for dependent samples was used.

RESULTS

The study involved 49 patients (26 men (53.1%) and 23 women (46.9%), average age 65 (59; 68) years) with acute ischemic stroke in the middle cerebral artery, discharged from the Regional Vascular Center of the Tomsk Regional Clinical Hospital after stage I of medical rehabilitation. The population was divided into two groups.

Group 1 (n = 32) received rehabilitation treatment at the stage II of rehabilitation at the Branch of Research Institute of Balneology and Physiotherapy of the Siberian Federal Scientific Clinical Center of Federal Medical Biological Agency. Group 2 (n = 17) was discharged for outpatient follow-up at the place of residence. After stage I of medical rehabilitation, the total score of the assessment scales in the study population indicated a moderate neurologic deficit ($_{NIHSSday14}$ = 4 (3; 8) points; FMA_{day14} = 196 (179; 200) points) and moderate disability (mRS_{day14} = 3 (2; 4) points). To determine the normal values of serum BDNF for a given age population, a comparison group was created, consisting of 50 individuals without stroke, comparable to the study sample by gender, age, and risk factors for developing cerebrovascular diseases (Table 1).

Groups I and II on day 14 after stroke were equivalent in terms of the severity of neurologic deficit and functional independence (Table 2). Group I patients after the second stage of medical rehabilitation using traditional approaches to the restoration of motor functions of the limbs showed pronounced regression of neurologic deficit according to the NIHSS ($p_{day14-90}$ = 0.002) and FMA ($p_{day14-90}$ = 0.003) scales, as well as improved functional independence according to the mRS scale ($p_{day14-90}$ = 0.009). Group II patients discharged for outpatient follow-up also showed a decrease in the total score on the NIHSS ($p_{day\ 14–90}$ = 0.025) and mRS ($p_{day\ 14–90}$ = 0.011) scales, whereas a significant increase in the total score on the FMA scale ($p_{day\ 14–90}$ = 0.406) was not observed (Table 2).

Table 1

Clinical and demographic characteristics of the population

Parameter	Group I	Group II	Comparison group	p
Average age, years, *Me* (Q_1 ; Q_3)	62 (57; 67)	66 (61; 68)	63 (56; 65)	0.817
Gender				
Male, abs. (%)	17 (53%)	9 (53%)	29 (58%)	0.876
Female, abs.(%)	15 (47%)	8 (47%)	21 (42%)	0.902
Arterial hypertension (%)	32 (100%)	17 (100%)	37 (74%)	0.914
Duration of hypertension, years, *Me* (Q_1; Q_3)	11 (10; 15)	10 (10; 15)	6 (5; 9)	0.892
Ischemic heart disease (%)	15 (47%)	7 (41%)	11 (22%)	0.789
Myocardial infarction (%)	7 (22%)	4 (23%)	0	0.231
Atrial fibrillation (%)	5 (15%)	4 (23%)	0	0.190
Stenting and artificial heart valves (%)	2 (4%)	1 (6%)	0	0.380
Obesity (%)	21 (65%)	13 (76%)	28 (56%)	0.785
Dyslipidemia (%)	27 (84%)	13 (76%)	43 (86%)	0.872
Diabetes mellitus (%)	8 (25%)	2 (12%)	14 (28%)	0.638
Duration of diabetes mellitus, years, *Me* (Q_1; Q_3)	8 (5; 10)	12 (5; 20)	7 (4; 10)	0.742
Smoking (%)	18 (56%)	9 (53%)	32 (64%)	0.823
BDNF level, day 14, *Me* (Q_1; Q_3)	2,768.0 (2,009.0; 3,652.0)	2,224.0 (1,302.0; 4,497.0)	4,273.0 (2,221.0; 5,251.0)	0.072
BDNF level, day 90, *Me* (Q_1; Q_3)	2,175.0 (1,730.0; 2,739.0)	881.1 (231.9; 1,483.5) *&	4,273.0 (2,221.0; 5,251.0)	0.000
Stroke subtype according to TOAST criteria				0.204
Large artery atherosclerosis (%)	5 (16%)	2 (12%)		
Cardiac embolism (%)	4 (12%)	5 (29%)		
Small vessel occlusion (%)	0 (0%)	0 (0%)		
Stroke of undetermined etiology (%)	23 (72%)	10 (59%)		
Affected hemisphere of the brain				0.401
right (%)	16 (53%)	11 (65%)		
left (%)	15 (47%)	6 (35%)		

Significant differences in comparison: * with group I; & with the comparison group

Table 2

Analysis of clinical parameters between groups I and II according to the NIHSS, FMA, and mRS scales, *Me* (Q_1; Q_3)

Parameter	Group I	Group II	$p_{\text{groups I – II}}$
NIHSS $_{\text{day14}}$	4 (3; 4)	3.5 (2; 9)	0.688
NIHSS $_{\text{day90}}$	3 (2; 4)	3 (2; 9)	0.176
$p_{\text{day 14–90}}$	0.002	0.025	
FMA$_{\text{day 14}}$	191 (177; 201)	201 (169; 203)	0.612
FMA$_{\text{day 90}}$	199 (190; 215)	203 (172; 204)	0.245
$p_{\text{day 14–90}}$	0.003	0.406	
mRS$_{\text{day 14}}$	3 (2; 3)	2 (2; 3)	0.351
mRS$_{\text{day 90}}$	2 (1; 2)	2 (1; 3)	0.143
$p_{\text{day 14–90}}$	0.009	0.011	
ΔmRS	–1 (–2; 0)	0 (–1; 0)	0.047
ΔNIHSS	–2 (–3; –1)	–1 (–2; 0)	0.043
ΔFMA	8 (6; 14)	3 (1; 4)	0.032
ΔFMA$_{\text{arm}}$	6 (4; 9)	2 (1; 3)	0.041
ΔFMA$_{\text{leg}}$	4 (2; 6)	2 (1; 4)	0.015

A comparative analysis of changes in the values of clinical scales in the study groups between the observation points showed that the increase in points on the ΔFMA scale ($p_{groups\ I-II}$ = 0.032) and regression of total points on the ΔNIHSS ($p_{groups\ I-II}$ = 0.043) and ΔmRS ($p_{groupsI\text{-}II}$ = 0,047) scales in the patients undergoing physical rehabilitation significantly exceeded those in the patients receiving outpatient follow-up.

A detailed assessment of upper and lower extremity motor functions according to the FMA scale revealed a more pronounced increase in group I compared with group II ($p_{groups\ I\text{–}II}$ = 0.041 and $p_{groups\ I\text{–}II}$ = 0.015, respectively) (Table 2).

In terms of the BDNF level, no significant differences were found between the serum BDNF level in the stroke patients from groups I and II on day 14 and individuals from the comparison group (Table 1, Fig. 1).

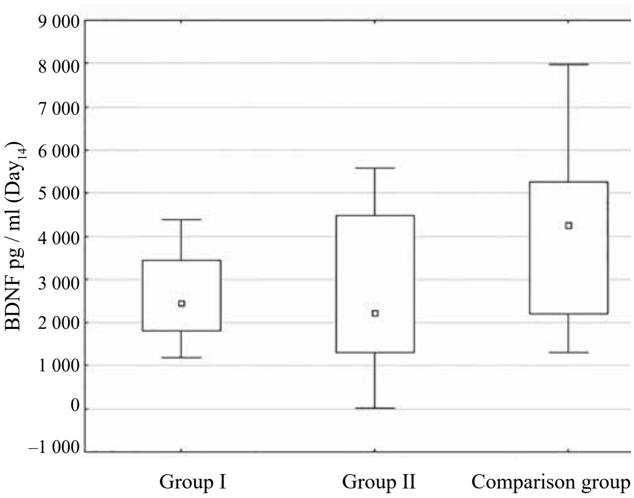

Fig.1. BDNF level in the patients of the comparison group and groups I–II on day 14 after stroke

At the same time, the concentration of the brain plasticity biomarker, which is responsible for neuronal survival and functional recovery after stroke, significantly decreased by the end of the early recovery period in the patients receiving outpatient follow-up in group II ($p_{day14\text{-}day90\_gr.\ II.}$ = 0.002). In the group of patients undergoing rehabilitation, on the contrary, no decrease in the factor level ($p_{day14\text{-}day90\_gr.I.}$ = 0.613) was noted. In this regard, on day 90 of the study, the concentration of BDNF in group II became significantly lower than in other groups, which still did not differ from one other (Table 1, Fig. 2).

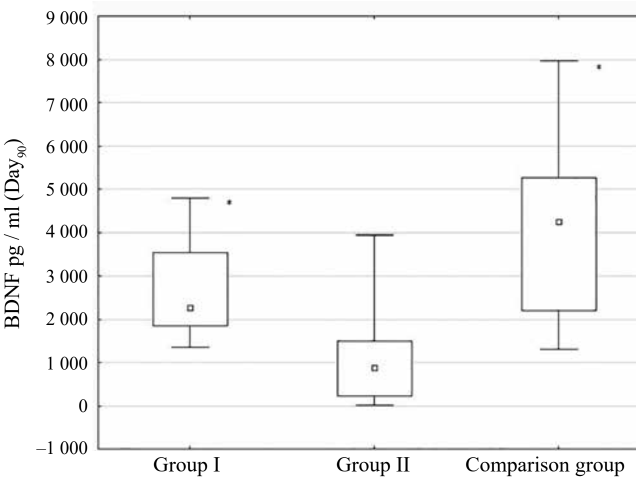

Fig. 2. BDNF level in the patients of the comparison group and groups I–II on day 90 after stroke: * significant differences compared with group II

DISCUSSION

It is known that the level of BDNF in the blood serum increases in response to ischemic damage to the brain tissue and reaches its maximum concentration on average on day 14 from the onset of stroke [14, 15]. The absence of differences between the BDNF level in the study groups on day 14 of the disease and in the comparison group, comparable in terms of sex, age, and risk factors for stroke, can be interpreted as a factor of a favorable prognosis for functional recovery. However, a comparative analysis of the study population in the dynamic follow-up showed that the patients who received motor rehabilitation in the early recovery period had greater regression of neurologic deficit on the NIHSS scale and a positive trend on the FMA scale.

In addition, in group I, there was not only better recovery of the motor function of the limbs, but also a more pronounced increase in the functional activity – ΔmRS ($p_{group\ I\text{-}II}$ = 0.047) in comparison with the patients in group II. The data indicate the clinical effectiveness of rehabilitation measures using traditional approaches to restoring motor functions of the limbs.

The study of neurobiological markers showed that the concentration of BDNF also changes depending on the implementation of rehabilitation procedures or their absence. In the patients in group I, the level of serum BDNF did not significantly change between day 14 and 90 after stroke, maintaining a high concentration and not differing from those in the comparison group. The opposite results were obtained in group II, where the level of the biomarker steadily decreased and was lower at the end of the early recovery period than in the comparison group.

Numerous fundamental studies have shown the role of BDNF in the implementation of brain plasticity processes due to the activation of neurogenesis, migration of nerve cells, remyelination of axons, as well as prevention of the effect of proinflammatory cytokines and a decrease in neuronal apoptosis [20, 21]. The key role of BDNF in the regulation of memory and motor learning mechanisms through the effect of long-term potentiation was demonstrated [22, 23]. In studies on experimental models of ischemic stroke in animals, it was shown that the expression of this neurotrophin increased during physical rehabilitation due to the activation of the motor cortex and improved the replenishment of motor deficits [24].

We found better recovery of motor function and functional independence in group I, which corresponded to changes in the FMA, NIHSS, and mRS scales. At the same time, in the group of patients who went through the stage II of medical rehabilitation, where a change in the FMA scale was observed, and changes in the NIHSS and mRS scales were more pronounced, the BDNF parameter remained at the same level.

Apparently, the only possible explanation for the improvement of motor function and functional independence was physical rehabilitation in these patients, which, in turn, was also accompanied by maintenance of the BDNF level. In our opinion, this suggests that induction of the activity-dependent pathway of BDNF expression and maintenance of its relatively high concentration during the stage II of medical rehabilitation were the main mechanisms that predetermined a favorable clinical and functional outcome.

CONCLUSION

The results of the study demonstrate the clinical effectiveness of the stage II of comprehensive rehabilitation of patients in the early period of stroke recovery and suggest that successful neurorehabilitation is closely related to an increase in the BDNF level during rehabilitation. This makes BDNF a potential marker for assessing rehabilitation effectiveness. The use of rehabilitation methods that increase the level of BDNF is promising.

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Kazakov S.D. – collection of material, drafting of the manuscript. Koroleva E.S. – conception and design. Brazovskaya N.G. – statistical processing of data. Zaitsev A.A. – analysis or interpretation of data. Ivanova S.A. – critical revision of the manuscript. Alifirova V.M. – final approval of the manuscript for publication.

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