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Low Concentration of BDNF in the Acute Phase of Ischemic Stroke as a Factor in Poor Prognosis in Terms of Functional Status of Patients

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEFG 1,2 Anetta Lasek-Bal
ABCDEFG 3 Halina Jędrzejowska-Szypułka
ABCFG 1 Jagoda Różycka
BCFG 4 Wiesław Bal
EFG 5 Michał Holecki
ACDG 5 Jan Duława
ACDG 3 Joanna Lewin-Kowalik

1 Department of Neurology, Medical University of Silesia Hospital No. 7, Professor Leszek Giec Upper Silesian Medical Centre, Katowice, Poland
2 School of Health Sciences, Medical University of Silesia in Katowice, Katowice, Poland
3 Department of Physiology, School of Medicine, Medical University of Silesia in Katowice, Katowice, Poland
4 Department of Radiation Oncology and Chemotherapy, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice, Poland
5 Department of Internal Medicine and Metabolic Diseases, Medical University of Silesia Hospital No. 7, Professor Leszek Giec Upper Silesian Medical Centre, Katowice, Poland

Corresponding Author: Anetta Lasek-Bal, e-mail: alasek@gcm.pl
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Background: According to recent studies, brain-derived neurotrophic factor (BDNF) probably plays a role in development of cerebral ischemia and can be significant for the prognosis of improved mobility after stroke. The aim of this prospective study was to evaluate the blood concentration of BDNF during the 1st day of first-ever ischemic stroke and find a potential association between BDNF concentration and the neurological status in the acute period, as well as between BDNF and the functional status in the sub-acute phase of stroke.

Material/Methods: The prospective study involved 87 patients aged 39–99 years (42 women, 45 men) with first-in-life complete ischemic stroke.

All study subjects underwent analysis as follows: BDNF blood concentration and neurological status according to NIHSS on the 1st day of stroke, comorbidities, etiological type of ischemic stroke by ASCOD, and functional status on the 14th and 90th day after the onset according to mRankin scale.

Results: Mean concentration of BDNF in the study group was 9.96 ng/mL±5.21, median 10.39 ng/mL. Patients aged ≤65 years (25 individuals) had a significantly higher mean concentration of BDNF (11.94 ng/mL±4.46; median 12.34 ng/mL) than the older subjects (62 individuals) with a mean concentration of 9.17 ng/mL±5.32 (median 8.66 ng/mL).

The mean score by mRankin scale on the 90th day was significantly higher among patients with lower concentrations of BDNF on the 1st day of stroke, which reflects their poorer functional status.

The functional status on the 90th day was significantly worse (3–6 points by Rankin scale) in patients who had BDNF below the mean value in the acute phase of stroke.

The independent factors for poor functional status of patients on the 90th day after stroke were a score >4 points by NIHSS (RR 1.14; 95% CI: 1.00–1.31; p=0.027) and the concentration of BDNF below the mean value (assessed on the 1st day of stroke) (RR 14.49; CI 4.60–45.45; p=0.000).

Conclusions: The neurological status and concentration of BDNF on the 1st day of ischemic stroke are independent prognostic factors in medium-term observation.

Reduction in the concentration of BDNF in the acute phase of stroke is a factor for poor prognosis in terms of the functional status of patients on the 90th day after onset.

MeSH Keywords: Brain-Derived Neurotrophic Factor • Prognosis • Stroke

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Background

Development and survival of neurons in the central nervous system are regulated by many extracellular factors. Neurotrophins play a significant role in the proliferation, migration, and phenotypic differentiation of cells (neurogenesis) and ensure their functional and structural integrity. Neurotrophins include nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin 4/5 (NT4/5) [1,2]. All of them bind to p75NTR with a relatively low affinity; however, they bind more selectively and with a greater affinity to Trk receptors [3]. BDNF acts on cells mainly through the Trk B receptor, and to a lesser extent through p75NTR, and facilitates neuronal survival and growth, modulates synaptic response, and is responsible for synaptic plasticity of neurons [4]. Although the primary function of neurotrophic factors is to control the processes of differentiation and survival of cells in the nervous system, they are also produced by cells of the immune system. In a healthy brain, neurons are the major source of and a target point for neurotrophic factors; under pathological conditions, additional synthesis is possible due to fraction of peripheral blood cells (mononuclear cell and T and B lymphocytes), which can compensate for the relative lack of BDNF in the nervous system [1,5]. The greatest amounts of BDNF are found in the areas responsible for memory and learning, mainly in the hippocampus and in the associative cortex. The correlation between the level of BDNF and neurodegenerative diseases (Alzheimer's, Parkinson's, Huntington's, and various dementias), depression, and obsessive-compulsive disorders has been widely studied [1,6,7]. It is believed that the presence of a specific polymorphism of BDNF is a factor determining the model of neurological damage and the possibility of neurological improvement after mechanical injury and ischemic damage, and in autoimmune diseases. BDNF concentration correlates with the degree of vasogenic damage to white matter of the brain. According to recent studies, BDNF genotype plays a role in development of cerebral ischemia and is significant for the prognosis of improved mobility after stroke [8].

The aim of this prospective study was to evaluate the blood concentration of BDNF during the first day of first-ever ischemic stroke. Furthermore, we tried to find a potential association between BDNF concentration and the neurological status in the acute period as well as between BDNF and the functional status in the sub-acute phase of stroke. To the best of our knowledge, this is the first prospective study to assess the role of BDNF concentration in the course of stroke and its effect on post-stroke disability prognosis.

Material and Methods

The prospective study (in the period from June 2014 to April 2015) involved 87 patients aged from 39 to 99 (42 women, 45 men) with first-in-life complete ischemic stroke diagnosed according to the WHO criteria, with an acute ischemic focus revealed in neuroimaging procedures (CT and/or MRI of the head) [9]. All participants were hospitalized from the first day of onset of stroke symptoms. Patients who had symptoms of transient ischemic attack (TIA) were excluded.

All study subjects underwent analysis in terms of the following:

- patient age at the time of first-ever ischemic stroke;
- etiological type of ischemic stroke by ASCOD [10];
- presence of conditions/comorbidities such as: arterial hypertension, atrial fibrillation, coronary heart disease, diabetes mellitus and dyslipidemia; >70% of atherosclerotic carotid artery stenosis (ipsilaterally to the ischemic focus in the brain);
- type of treatment used on the 1st day of stroke (including intravenous (IV) and intraarterial (IA) thrombolytic therapy and thrombectomy);
- neurological status on the 1st day of stroke according to NIHSS (National Institutes of Health Stroke Scale) [11];
- functional status on the 14th and 90th days after the onset according to mRankin scale [12];
- BDNF blood concentration on the 1st day of stroke: blood was collected in an amount of 10 mL per EDTA tube; after 15-min centrifugation (1500 RPM) plasma concentration of BDNF was assessed with the use of ELISA method (human BDNF by BioVender).

Mean concentration of BDNF in the whole group was assessed as well as in subgroups formed according to age (≤65 and >65), gender, neurological status on the 1st day of stroke by NIHSS (≤4 points *vs.* >4 points), functional status by mRankin scale on the 14th and 90th days (0–2 points indicates independence in everyday life and 3–6 points indicates a significant degree of dependence on the caregiver, or death), and in relation to the category of stroke by ASCOD. Comparisons were made between the subgroups.

Multivariate analysis was performed to determine independent factors of unfavorable prognosis (3–6 points on mRankin scale) on the 14th and 90th days after stroke. The following parameters were analyzed: age, gender, NIHSS score (≤4 points or >4 points), arterial hypertension, diabetes, coronary heart disease, atrial fibrillation, dyslipidemia, >70% stenosis of the carotid artery, and type of treatment used on 1st day of stroke (thrombolysis IV or IA and/or thrombectomy).

The diagnosis of hypertension was consistent with the recommendation by the Polish Society of Cardiology [13]; diabetes

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Table 1. Mean score by mRankin scale on the 14th and 90th day after stroke according to the concentration of BDNF measured on 1st day of stroke.

	BDNF <mean value n=42	BDNF ≥mean value n=45	P
mRS 14	2.78±1.96 [median 3] min 0 max 6	2.37±1.94 [median 2] min 0 max 6	0.3148
mRS 90	2.76±1.64 [median 3.0] min 0 max 6	1.31±1.53 [median 1.0] min 0 max 6	0.0000

mRS ^{14} – modified Rankin scale on 14th day of stroke; mRS ^{90} – modified Rankin scale on 90th day of stroke.

mellitus was diagnosed according to the criteria of the Polish Diabetes Association [14]; dyslipidemia was defined as total cholesterol serum level >200 mg/dl (>5.18 mmol/L); or LDL-cholesterol serum level >100 mg/dl (2.59 mmol/L), or HDL cholesterol serum level <35 mg/dL(0.91 mmol/L) or triglyceride serum level >135 mg/dL (1.53 mmol/L).

The degree of carotid artery stenosis was rated according to NASCET criteria [15].

All statistical analyses were performed using the STATISTICA 8.0 PL software. Chi-square tests were used for categorical variables. The Mann-Whitney U test was used to compare the study groups and subgroups for the nonparametric distribution of some of the parameters. The Kruskal-Wallis one-way analysis of variance was used in the comparison of subgroups according to ASCOD scale. Finally, analysis was performed using a single and multi-factorial method of nonlinear estimation – logistical regression (STATISTICA 5.0PL) – to identify independent factors for post-stroke disability on the 14th and 90th days following stroke. P<0.05 was considered statistically significant.

The consent to conduct the study was obtained from the Ethics Committee of the Medical University of Silesia.

Results

The study included 87 patients aged 71.7±11.8 (median 74; min 39, max 99 years old).

73 (83.9%) individuals were suffered with arterial hypertension, 25 (28.73%) with diabetes mellitus, 39 (44.82%) with coronary heart disease, 18 (24.13%) with atrial fibrillation. In 21 patients dyslipidemia was diagnosed and in 17 (19.54%) stenosis of ipsilateral carotid artery was diagnosed. Twelve (13.79%) individuals were treated with IV thrombolysis, including 1 patient with subsequent thrombectomy and other with intraarterial thrombolysis. Seventy-three patients (83.9%) disqualified from thrombolysis and thrombectomy received antiplatelet therapy (aspirin in daily dose of 300 mg or 75 mg clopidogrel); 2 individuals (2.29%) intravenous heparin because of progressive stroke.

Mean concentration of BDNF in the study group was: 9.96 ng/mL±5.21; median 10.39 ng/mL; while 42 patients had their levels of BDNF below the mean value for the study, in 45 patients BDNF concentration was above the mean value. The comparison between the mean concentrations of BDNF in men and women showed no significant differences (10.16 ng/mL±4.94 *vs.* 9.77 ng/mL±5.51 respectively; p=0.6835). Patients aged ≤65 (25 individuals) had a significantly higher mean concentration of BDNF (11.94 ng/mL±4.46; median 12.34 ng/mL; min 1.34 ng/mL, max 17.27 ng/mL) than the older subjects (62 individuals) with a mean concentration of 9.17 ng/mL±5.32 (median 8.66 ng/mL; min 0 ng/mL, max 18.66 ng/mL; p=0.0346).

Patients with mild neurological deficits (≤4 points by NIHSS) on the 1st day of stroke did not differ significantly in terms of mean concentration of BDNF (9.33 ng/mL±5.04) from those with >4 points by NIHSS (10.85 ng/mL±5.40; p=0.1788).

There were no significant differences in mean BDNF concentration between the patients who functioned independently (0–2 points by mRankin scale) on the 14th day following stroke and the patients who required assistance or died (3–6 points by mRankin scale); 9.98 ng/mL±4.98 *vs.* 9.92 ng/mL±5.70, respectively; p=0.9611.

There were no significant differences in mean score by mRankin on the 14th day between patients with reduced *vs.* mean or increased concentration of BDNF on the 1st day of stroke. However, mean score by mRankin scale on the 90th day was significantly higher among patients with lower concentration of BDNF on the 1st day of stroke, which reflects their worse functional status (Table 1).

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Table 2. The mRankin scale on the 90th day following stroke according to the concentration of BDNF on the 1st day of stroke.

mRankin	0	1	2	3	4	5	6
BDNF < mean value n (%)	4 (9.52%)	7 (16.67%)	4 (9.52%)	16 (38.10%)	5 (11.90%)	3 (7.14%)	3 (7.14%)
BDNF ≥ mean value n (%)	15 (33.33%)	15 (33.33%)	10 (22.22%)	2 (4.44%)	0	0	3 (6.67%)
p	0.0072	0.0739	0.1073	0.0001	0.0171	0.0681	0.9302

The functional status on the 90th day was significantly worse (3–6 points by Rankin scale) in patients who had BDNF below the mean value in the acute phase of stroke (Table 2).

There were no statistically significant differences between the mean concentrations of BDNF in patients categorized according to etiological classification of stroke (ASCOD – A: atherosclerosis, S: small vessel disease, C: cardiac pathology, O: other causes, D: dissection) (p=0.3114).

Multivariate analysis demonstrated that the independent factors for poor short-term prognosis (14th day) after stroke (3-6 points by mRankin scale) include the neurological status on the first day of onset corresponding to >4 points by NIHSS (CI 3.79 [1.44–10.02], p=0.0063) and the presence of coronary heart disease (3.0 CI [1.14–7.93] p=0.0245).

However, independent factors for poor functional status of patients on the 90th day after stroke included a score >4 points by NIHSS (RR 1.14; 95% CI: 1.00–1.31; p=0.027) and the concentration of BDNF below the mean value in the study (assessed on the 1st day of stroke) (RR 14.49; CI 4.60-45.45; p=0.000).

Discussion

Brain-derived neurotrophic factor, a mammalian neurotrophin, has recently been the object of interest due to its various effects within the process of neurogenesis, prevention of neurodegeneration, and promotion of neuroplastic processes. BDNF acts on cells mainly through the Trk B receptor, and to a lesser extent through p75NTR. These receptors activate many intracellular signaling pathways, which in turn activate MAPK, PI3K, and PLCg. Thus, BDNF acts on the energy resources of nerve cells, affects the development and function of the nervous system, and, in case of cell damage, inhibits apoptosis and promotes cell survival [8].

Increasing research is focussing on the participation of BDNF in the pathogenesis of mental disorders. Stress, inducing depression, anxiety, and other psychiatric disorders, interferes with the function of BDNF in limbic structures (the hippocampus and frontal lobes) associated with the emotional sphere. According to the neurotrophin hypothesis for depression, mood dysregulation and anxiety are associated with reduced levels of BDNF and antidepressant treatment reduces behavioral disorders through its increased concentration. It is likely that a similar mechanism is responsible for the development of post-stroke depression.

The presence of BDNF in many brain structures and its pleiotropic effect encouraged us to evaluate the role of that neurotrophin in the processes associated with ischemia of the nervous tissue. Interesting results provided by the Framingham study showed that decreased levels of BDNF in the blood increase the risk of stroke and TIA (HR 95%, CI: 1.11–2.03, p=0.008) [3]. It was found that the G196A polymorphism in the BDNF gene is associated with a higher probability of acute cerebrovascular incident [16]. Low concentrations of BDNF in the blood were observed in patients with risk factors for stroke, such as coronary artery disease, acute coronary syndrome, diabetes mellitus, metabolic syndrome, obesity, and physical inactivity [17–19]. In the present study, significantly lower levels of BDNF were observed in patients over 65 years of age. Older age is an important risk factor for stroke and a predictor of poorer prognosis.

It has not been established whether the concentration of BDNF is important for the course of acute ischemic stroke or post-stroke neurological deficit. Animal studies have demonstrated the beneficial effect of BDNF to limit the brain infarction area, which was associated with a better prognosis in terms of motor function [20,21]. The present study did not show any significant association between BDNF blood concentrations, the neurological status, and the functional status in the acute phase of stroke. BDNF probably does not play a key role in that phase of the disease, at least to such an extent sufficient to allow the assessment through the analysis of the clinical status of patients and to affect their physical ability to function in everyday life. Lower levels of BDNF in the blood in patients during the acute stroke phase are associated with significantly worse functional status on the 90th day after the onset. Moreover, lowered concentration of BDNF, apart from neurological status >4 points by NIHSS, proved to be an independent

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factor for poor prognosis. It appears that BDNF may play an important role in the processes reversing negative effects of cerebral ischemia; its decreased concentration may inhibit the effect of repair within brain structures. BDNF is involved in structural remodeling, neuronal plasticity, and synaptic restructuring, and is promising as a candidate molecule underlying the structural changes associated with ischemia damage, and as a potential target for cerebral ischemia injury [22–24].

Positive effects of high concentrations of BDNF have been reported to limit the extent of ischemic lesions in the white matter of the brain in subjects with risk factors for cardiovascular diseases [3,25,26]. Ischemic areas around cerebral ventricles result from neuronal and/or vascular injury and follow hypoperfusion, demyelination, neuronal loss, and gliosis in the area of deep small perforating cerebral arteries [25,27]. They are formed as a result of chronic ischemia of the nervous tissue. Little is known about the role of BDNF in shaping the area of acute ischemia of the nervous tissue and in the course of disease. As shown by Santhanam et al., BDNF promotes the production of prostaglandin I2 (PGI2) while promoting vasodilation. Increased concentration of PGI2 in the arterial wall activates pro-survival signaling by activation of peroxisome proliferator-activated receptor delta (PPAR). This in turn may increase the resistance of cerebral circulation against injury [28].

Authors still try to identify targets and mechanisms for acute stroke and protective agents against consequences of ischemic brain damage [29].

Many researchers attribute the role of the novel risk marker of cerebrovascular disease to BDNF and believe that in the future BDNF may be used to stratify the risk of stroke and TIA.

The results of the present study may indicate the importance of BDNF as a biomarker of repair processes limiting the effects of brain ischemia. Subjects with higher levels of BDNF in the acute phase of stroke have a greater chance of improvement in terms of independence after stroke.

Limitations

A patient's status before the onset of stroke and complications during hospitalization, including pulmonary embolism and pneumonia, have an impact on the degree of post-stroke disability and death, which was not included in the analysis and was a limitation of the study.

Conclusions

The neurological status and concentration of BDNF on the 1st day of ischemic stroke are the independent prognostic factors in medium-term observation.

Reduction in the concentration of BDNF in the acute phase of stroke is a factor for poor prognosis in terms of the functional status of patients on the 90th day after onset.

Further studies are required to determine the role of BDNF in the process of acute cerebral ischemia and to explore its consequences.

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