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Research Article

Association Between Serum BDNF Level and Cognitive-Linguistic Outcomes in Aphasic Stroke

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Abstarct

Objective: This study examines the association between serum Brain-Derived Neurotrophic Factor (BDNF) level and cognitive-linguistic outcomes in patients with post-stroke aphasia.

Design: A total of 119 patients with first left hemisphere stroke were divided into two groups: aphasia (n=66) and non-aphasia (n=53). Serum BDNF level, speech language pathology diagnosis, and functional independence measure (FIM) were assessed in all patients. Aphasia severity level, Functional Communication Measure (FCM) spoken language comprehension, and FCM language expression were also tested in aphasic patients. The relationship between serum BDNF level and cognitive-linguistic outcomes were analyzed by Spearman correlation.

Results: The serum BDNF level of aphasic patients had a positive correlation with total FIM (r=0.284, p=0.021) at admission. At discharge, the serum BDNF was related to cognitive subtotal FIM (r=0.284, p=0.021), comprehension (r=0.265, p=0.032), expression FIM (r=0.308, p=0.012), memory FIM (r=0.266, p=0.031), motor subtotal FIM (r=0.290, p=0.018), and total FIM (r=0.315, p=0.010). Similarly, Spearman correlation analysis revealed a correlation between serum BDNF and FCM spoken language expression level changes (r=0.255, p=0.038) and severity of aphasia level changes (r=0.282, p=0.022). With regards to

serum concentrations of BDNF and non-aphasic patients' function, only expression at admission showed significant difference (r=0.339, p=0.013).

Conclusion: Our findings suggest that serum concentrations of BDNF may help to predict the cognitive-linguistic outcomes in aphasic stroke patients during acute rehabilitation.

Keywords: BNDF; Aphasia; Stroke; Cognitive-linguistic outcome

What is known: due to language deficit, it has been challenging to measure cognitive function.

What is new: this is the first study to investigate relationship between serum BDNF cognitive-linguistic outcomes in aphasic stroke patients during acute rehabilitation, and this findings may provide insight into the biological mechanism of recovery in post-stroke aphasia and may help to develop personalized treatment plans.

Introduction

Stroke patients with aphasia suffer from wide range of language impairment including the auditory comprehension, verbal expression, reading, writing, or functional communication. Aphasia is also associated with an individual's cognition, emotion, self-image, well-being, relationships, employment, and quality of life [1,2]. Language processing has been shown to be controlled by cognitive-linguistic function, such as attention, executive function, and memory [3]. Fillingham, et al. [4], demonstrated that aphasic patients with impairment in recognition memory and attention had poor response to anomia treatment. Similarly, Nicholas, et al. [5], reported that aphasia with poor executive function had a worse response to a treatment program. Therefore, it is important to identify and treat cognitive deficit in aphasia. However, due to language deficit, it has been challenging to measure cognitive function. Serum biomarkers have the potential to provide important supplementary measure to detect cognitive impairment and insight for personalized target for treatment [6].

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family of growth factors, which implicate neuronal differentiation, maturation, survival, synapse information [7]. It also has been found to play a central role in neuroprotection and neuronal repair, by promoting neurogenesis and angiogenesis [8]. In the central nervous system (CNS), BDNF is widely expressed in the hippocampus, cortex, and basal forebrain, linking to cognition, learning, and memory [9]. Galit, et al. [10], demonstrated there was a relationship between higher serum BDNF concentrations and decreased risk for dementia in healthy adults, especially in older women, in a community-based cohort study of 2131 participants (mean aged 72 years). Similar results were found in a 10-year longitudinal study where low serum BDNF levels were associated with a higher risk of stroke and reduced cognitive function in a stroke-free sample of 3440 men and women (mean aged 65 years) [8]. Acute serum BDNF levels showed a positive correlation with cognitive function, as well as with memory, at 6 months in Traumatic Brain Injured (TBI) patients [11]. However, very few studies revealed the relationship between serum BDNF concentrations and cognitive-linguistic function outcomes in aphasic patients.

This research was designed to explore the relationship between serum BDNF levels and cognitive-linguistic outcome in aphasic patients during acute inpatient rehabilitation. It may provide insight to design personalized rehabilitation plans for aphasic stroke patients.

Materials and Methods

Participants

This retrospective study screened 359 consecutive stroke patients admitted to hospital from March 20, 2014 to August 11, 2015 and was approved by the Institutional Review Board. Patients from our rehabilitation unit with a primary diagnosis of acute cerebrovascular accident of the left hemisphere were included, and patients were excluded if they had prior stroke history, length of hospitalization less than one week, or a diagnosis of profound dysfunction in severity of aphasia. A total of 119 patients were included in this research. They were divided into two groups (aphasia group or non-aphasia group) according to a diagnosis by speech language pathology (as shown in Figure 1). All patients underwent rehabilitation in our rehabilitation unit throughout their inpatient stay. Our unit team is comprised of physicians, speech and language therapists, occupational therapists, physiotherapists, dieticians, and nurses. The team provided personalized comprehensive care and rehabilitation to every patient. The demographic and clinical data of enrolled subjects, including age, gender, Body Mass Index (BMI), preferred language, ethnicity, marital status, risk factors, stroke site, time from stroke onset to hospital admission, length of hospital stay, and discharge destination, were collected from medical records. The ethics committee of hospital has already approved this human study.

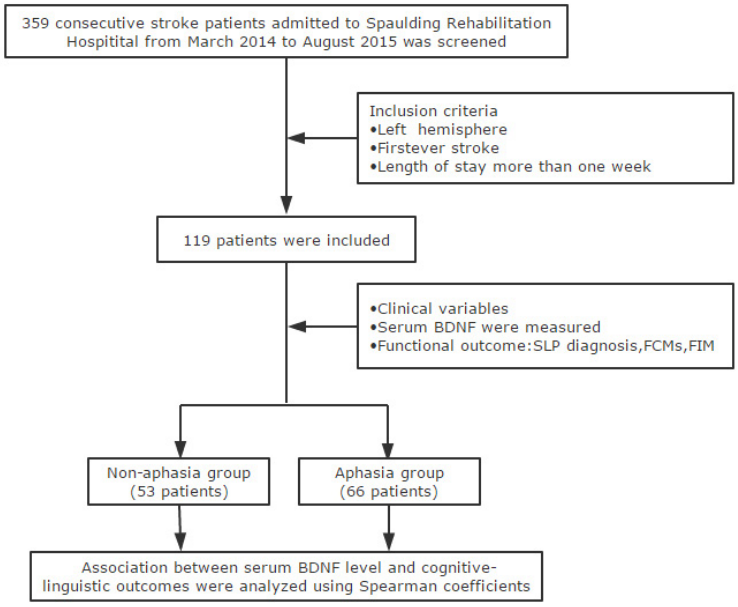

Figure 1: Flow chart

Functional outcome measurement

All subjects were assessed using speech language pathology diagnosis, American Speech-language-hearing Association's Functional Communication Measures (FCMs), and Functional Independence Measure (FIM) test by experienced therapists.

Speech language pathology diagnosis is a comprehensive diagnosis, including language (auditory comprehension, verbal expression, reading comprehension, written expression, motor speech, and voice) and cognitive-linguistic (attention, orientation, memory, problem solving, judgment, and executive function). There are ten levels, ranging from profound injury (level 1) to without function limit (level 10), in each item. The final level and category of aphasia is based on: 1. language and cognitive-linguistic results mentioned previously; 2. results of standardized tests, such as Western Aphasia Battery or Boston Diagnostic Aphasia Examination; 3. clinical judgment of a speech-language pathologist; and 4. medical diagnosis and imaging. The level of aphasia ranges from one (profound dysfunction) to ten (normal).

American Speech-Language Hearing Association's (ASHA) functional communication measures use seven-rating scales, ranging from least functional (level 1) to most functional (level 7). They describe different aspects of a patient's functional communication and swallowing abilities: spoken language comprehension, spoken language expression, reading, writing, motor speech, voice, swallowing, attention, memory, problem solving, augmentative/alternative communication, and pragmatics.

Functional Independence Measure (FIM) addresses the level of assistance needed by an individual required to carry out Activities of Daily Living (ADLs). The scale of FIM comprises two parts: motor skills (eating, grooming, bathing, dressing-upper body, dressing-lower body, toileting, bladder management, bowel management, bed/chair/wheelchair transfer, toilet transfer, tub/shower transfer, walk/wheelchair locomotion, stairs locomotion) and cognitive skills (comprehension, expression, social interaction, problem solving, memory). Each item has a grade from 0 (total assistance) to 7 (complete independence). Scores range from 18 (lowest) to 126 (highest), indicating level of function.

Since this was a retrospective study, there were some missing data. We chose only the integrated items as the results to get a more accurate analysis. In the speech language pathology diagnosis, we used scores of auditory comprehension, verbal expression, motor speech, attention, and severity level of aphasia; In FCMs, we got spoken language comprehension score and spoken language expression score as results.

Serum BDNF measurement

The serum from aphasia patients was collected on admission and then stored in polypropylene test tubes at -80 °C until used. Serum BDNF levels were analyzed using enzyme-linked immunosorbent assay (ELISA kit, R&D Quatikine, Minneapolis, USA). Data were analyzed using SPSS statistical software, version 21.0 (SSPS Inc, Chicago, IL). The data were expressed using mean, median, standard deviation, and percentile analysis. Significance was accepted at a 2-sided *p* value of less than 0.05.

The demographics and clinical characteristics were compared at baseline by independent t test for continuous variables (age, BMI, time from stroke onset to admission, days, and length of stay) and by Chi-square test or Fisher's exact test for categorical variables (preferred language, ethnicity, marital status, risk factors, stroke site, and discharge destination). The function between the two groups was tested by the Mann-Whitney U test. The relationships between serum BDNF and functional parameters were assessed using Spearman coefficients.

Results

Demographics and clinical characteristics

Descriptive statistics for demographics and clinical parameters of the two groups are summarized in Table 1. Of the 119 patients in this study, 66 (55.5%) had aphasia. A comparative analysis between the two groups showed similar baseline characteristics except stroke site and the time between onset to admission to rehabilitation hospital. The types of aphasia are shown in Table 2: mixed transcortical 19 (28.8%), global 12 (18.2%), anomic 10 (15.2%), Broca's 8 (12.1%), transcortical motor 3 (4.5%), Wernicke's 2 (3.0%), and undefined 12 (18.2%).

Characteristics	**Aphasic(n=66)**	**Nonaphasia(n=53)**	***P* value**
Age (years)	67.39±16.276	66.11±16.544	0.673
Body mass index (BMI, kg/m^2)	29.07±7.197	27.90±8.755	0.425
Gender (n)			
Male	37 (56.1)	30 (56.6)	0.953
Female	29 (43.9)	23 (43.4)	
Preferred language			
English	61 (92.4)	48 (90.6)	0.975
Not English	5 (7.6)	5 (9.4)	
Ethnicity (n)			
Hispanic or latino	2 (3.0)	3 (5.7)	0.802
Not Hispanic or latino	64 (97.0)	50 (94.3)	
Marital status			
Single	12 (18.2)	14 (26.4)	0.758
Separated or divorced	7 (10.6)	5 (9.4)	
Windowed	13 (19.7)	9 (17.0)	
Married	34 (51.5)	25 (47.2)	
Risk factors (n)			
Hypertension	51 (77.3)	43 (81.1)	0.607
Atrial fibrillation	16 (24.2)	6 (11.3)	0.071
Coronary artery disease	10 (15.2)	6 (11.3)	0.543
Diabetes mellitus	16 (30.2)	18 (27.3)	0.726
Current smoker	10 (15.2)	11 (20.8)	0.426
Stroke site (n)			
Supratentorial	60 (90.9)	34 (64.2)	0.000*

Infratentorial	5 (7.6)	19 (35.8)	
Both	1 (1.5)	0 (0.0)	
From onset to admission(days)	10.50±8.209	6.11±3.343	0.000*
Length of stay (days)	19.64±8.470	19.73±11.064	0.956
Discharge destination (n)			
Home	38 (57.6)	36 (67.9)	0.294
Skilled nursing facility(SNF)	27 (40.9)	15 (28.3)	
Acute hospital	1 (1.5)	2 (3.8)	
Values are represented as mean ± standard deviations or sample number and percentage.			

Table 1: Demographics and clinical characteristics.

Category	**Participants**
Mixed transcortical aphasia	19 (28.8)
Global aphasia	12 (18.2)
Anomic aphasia	10 (15.2)
Broca's aphasia	8 (12.1)
Transcortical motor aphasia	3 (4.5)
Wernicke's aphasia	2 (3.0)
undefined	12 (18.2)
Values are represented as sample number and percentage	

Table 2: Aphasia Classification.

Functional outcomes

Compared to those without aphasia, aphasic patients had lower scores in auditory comprehension (P=0.000), verbal expression (P=0.000), motor speech (P=0.000), cognitive FIM (P=0.000), and total FIM (P=0.000) both at admission and discharge, whereas attention and motor FIM were not statistically different (Table 3). The increase of verbal expression was significant between the two groups.

Serum BDNF and functional outcomes

Serum concentrations of BDNF in aphasic patients and non-aphasic patients were 21.19±6.912 ng/ml and 22.70±7.293 ng/ml, respectively. Spearman correlation showed associations between serum BDNF and aphasic patients' functional outcomes (Table 4). There was significant correlation between serum BDNF level and total FIM at admission (r=0.284, p=0.021). There was positive correlation among serum BDNF level and cognitive subtotal FIM scores (r=0.284, p=0.021), comprehension FIM scores (r=0.265, p=0.032), expression FIM scores (r=0.308, p=0.012), memory FIM sores (r=0.266, p=0.031), motor subtotal FIM scores (r=0.290, p=0.018), and total FIM scores (r=0.315, p=0.010) at discharge. Moreover, correlation coefficients between serum BDNF level and score of FCM spoken language expression changes and severity of aphasia were 0.255 (p=0.038), 0.282 (p=0.022), respectively. In non-

aphasic patients, serum concentration of BDNF was correlated only with expression at admission.

	Function outcome	Aphasic(n=66)	Nonaphasic(n=53)	P value
Admission	Auditory comprehension	5.0(3.0-7.0)	9.0(9.0-9.0)	0.000*
	Verbal expression	3.0(3.0-5.0)	9.0(9.0-9.0)	0.000*
	Motor speech	6.0(4.0-9.0)	9.0(6.2-9.0)	0.000*
	Attention	9.0(6.0-9.0)	7.0(5.0-9.0)	0.346
	Cognitive FIM	14.0(9.5-18.5)	22.0(18.5-25.0)	0.000*
	Motor FIM	33.0(15.5-42.5)	34.0(22.0-43.0)	0.342
	Total FIM	48.0(29.0-68.0)	59.0(42.5-69.0)	0.026*
Discharge	Auditory comprehension	6.0(4.0-7.0)	9.0(9.0-9.0)	0.000*
	Verbal expression	5.0(3.0-7.0)	9.0(9.0-9.0)	0.000*
	Motor speech	7.0(4.0-9.0)	9.0(7.0-9.0)	0.003*
	Attention	7.0(6.0-9.0)	9.0(6.0-9.0)	0.158
	Cognitive FIM	21.0(16.5-26.0)	28.0(24.5-32.0)	0.000*
	Motor FIM	54.0(33.5-65.0)	55.0(42.0-67.0)	0.475
	Total FIM	80.0(52.5-93.0)	89.0(70.5-101.5)	0.032*
Change	Auditory comprehension	0.0(0.0-1.0)	0.0(0.0-0.0)	0.056
	Verbal expression	1.0(0.0-1.0)	0.0(0.0-0.0)	0.002*
	Motor speech	0.0(0.0-1.0)	0.0(0.0-1.0)	0.966
	Attention	0.0(0.0-1.0)	0.0(0.0-1.0)	0.711
	Cognitive FIM	7.0(4.0-9.0)	6.0(3.5-8.0)	0.375
	Motor FIM	19.0(10.5-25.5)	21.0(12.0-28.5)	0.482
	Total FIM	24.0(19.0-37.0)	28.0(16.5-36.5)	0.574

Values are represented as median and interquartile range. **FIM:** Functional Independence Measure. *, P <0.050.

Table 3: Functional outcome.

Parameter	Admission			Discharge			Change		
	Function	r	P value	Function	r	P value	Function	r	P value
Spaulding SLP diagnosis									
Auditory comprehension	5.30±2.172	0.181	0.147	5.72±2.146	0.136	0.275	0.52±1.134	0.037	0.767
Verbal expression	2.99±1.814	0.148	0.234	4.67±1.959	0.177	0.156	0.82±1.158	0.049	0.694
Motor speech	6.19±2.277	0.099	0.43	6.56±2.391	0.047	0.71	0.40±2.335	0.072	0.564
Attention	7.12±2.574	-0.042	0.737	7.36±1.754	-0.003	0.978	0.26±1.928	0.135	0.278
Severity of aphasia	4.32±1.656	0.045	0.717	5.379±1.871	0.219	0.078	0.95±1.143	0.282	0.022*

FCM									
Spoken language comprehension	3.68±1.451	0.088	0.481	4.91±1.101	0.235	0.057	1.28±0.778	0.143	0.253
Spoken language expression	2.99±1.447	0.07	0.577	4.43±1.421	0.202	0.104	1.39±0.903	0.255	0.038*
FIM									
Cognitive subtotal	14.17±6.050	0.189	0.128	20.82±5.740	0.284	0.021*	6.65±4.028	0.091	0.467
Comprehension	2.89±1.426	0.096	0.442	4.16±1.376	0.265	0.032*	1.27±0.937	0.169	0.174
Expression	2.30±1.358	0.137	0.271	3.43±1.458	0.308	0.012*	1.13±0.875	0.199	0.109
Social interaction	4.15±1.800	0.186	0.135	5.73±1.342	0.071	0.569	1.57±1.745	-0.104	0.405
Problem solving	2.18±1.189	0.21	0.091	3.53±1.338	0.235	0.058	1.35±1.157	0.038	0.762
Memory	2.39±1.036	0.132	0.29	3.76±1.190	0.266	0.031*	1.36±0.987	0.167	0.18
Motor subtotal	31.41±15.628	0.241	0.051	50.39±20.109	0.29	0.018*	18.98±9.936	0.214	0.085
Total	48.03±20.593	0.284	0.021*	74.91±25.479	0.315	0.010*	26.87±1.522	0.24	0.053

Values are represented as mean ± standard deviations. Spaulding SLP diagnosis, Spaulding Rehabilitation Hospital speech-language pathology diagnosis. **FCM:** Functional Communication Measures; **FIM:** Functional Independence Measure. *, P <0.050.

Table 4: Spearman correlation coefficients between BDNF level and aphasic functional outcome.

Discussion

The current study aimed to evaluate the relationship between serum BDNF level and cognitive-linguistic outcome in aphasic stroke patients during acute inpatient rehabilitation.

Cognitive-linguistic impairment in left hemisphere stroke

Aphasia is a common after stroke affecting as many as 38% of stroke survivors [12]. Aphasia is an acquired impairment that affects spoken language expression, spoken language comprehension, written expression, or reading comprehension [13]. In the majority of people, the language network is located in the frontal, temporal, and parietal Perisylvian areas of the left hemisphere [14]. The present study compared the functional outcome in left hemisphere, first-ever stroke patients with and without aphasia. The results from this study have confirmed that aphasia patients have poor auditory comprehension, verbal expression, and motor speech.

Cognitive dysfunction frequently occurs in post-stroke patients. The prevalence of post-stroke cognitive impairment ranges from 20% to 80% [15]. Ischemic stroke patients suffer communicative disorders, increasing the risk of non-verbal cognitive deficits. Comprehensive assessment and rehabilitation are needed for these patients. Early prediction of patients' functional outcome is essential to set proper rehabilitation goals and to determine further rehabilitation plans. Literature also reports that cognitive function of post-stroke aphasia patients was inferior to that of patients without aphasia [16]. Our findings were consistent with previous studies, that cognitive FIM scores in aphasia patients showed significant differences compared to those of non-aphasia patients. Attention as a domain of cognition plays a pivotal role in language processing. One previous investigation reported that in 22 (19 patients had aphasia) participants with left-hemisphere stroke, all of them displayed at least one dysfunction in sustained, selective, or divided attention; however, they didn't show whether there were differences between patients with and without aphasia [17]. In our trial, the data show no significant differences between first-time left-hemisphere stroke participants with and without aphasia in attention function.

Associations of Cognitive-linguistic impairment and BDNF in acute rehabilitation

There are many screening instruments used to evaluate aphasic patients' function: Boston Diagnostic Aphasia Examination, Western Aphasia Battery, Cognitive Linguistic Quick Test, etc. They evaluate various perceptual modalities, processing functions, and response modalities. However, these tests do not directly reflect the biological mechanisms of brain recovery. BDNF as a nerve-growth protein plays important roles in synaptic plasticity, synaptic efficacy, neuronal connectivity, cell migration, glutamate release, and neuropeptide expression [18]. It acts via at least two receptors: one is a low-affinity nerve growth factor receptor (LNGFR, 75kDa); the other is a tropomyosin receptor kinase-B (TrkB) receptor (145kDa) [18]. Specifically for BDNF, LNGFR can promote Schwann cell migration near injury and active apoptotic signaling [19]. TrkB receptor is a high-affinity

receptor of BDNF attributed to the majority of trophic effects [18]. Cells that express TrkB are thymocytes, pyramidal cells in the hippocampus, motoneurons in the spinal cord, and almost all neurons in the developing brain, etc [20,21]. Via the high-capacity saturable transporter system, BDNF (27kDa) can cross the blood-brain barrier in both directions [7]; suggesting that serum BDNF reflects brain BDNF levels.

Bejot, et al. [22], have shown that neuronal expression of BDNF increases acutely after stroke as a pro-survival response and that BDNF levels correlate with the degree of functional survival. However, the association of serum BDNF with functional outcome after stroke has been controversial. Stanne, et al. [23], reported that low circulating concentrations of BDNF during the acute phase after stroke are associated with poor long-term functional outcome, as defined by a modified Rankin Scale score of 3-6 at three months follow-up, 3-5 at 7 years follow-up, and 2 at 7 years after ischemic stroke; although BDNF concentrations were not significantly associated with 3-month outcome. Conversely, another study reported a correlation of low serum BDNF with poor outcome at 3 months. Our previous study suggests that serum BDNF offers minimum predictive value for motor outcome during post-acute inpatient rehabilitation [24]. These discrepancies might be due to variations in clinical variables, patient populations, standard treatment, and genetic predisposition. Subgroup analysis would be necessary to uncover the most robust correlation. A study reporting the association between BDNF and verb naming suggested that BDNF might be one factor linked to the recovery of language [25]. Our observational study is the first to show that the serum BDNF level of aphasic stroke patients in the acute rehabilitation period has a positive correlation with improvement of aphasia severity and gain of FCM spoken language expression scores.

Our study also suggests that higher serum BDNF levels at admission correlate to better comprehension, expression, and memory outcomes at discharge. Aaron, et al. [26], point out that BDNF is important for cognitive performance. BDNF and its receptor (TrkB) are widely distributed and highly expressed throughout the CNS, especially in the cerebral cortex and hippocampus where they are implicated in memory formation and long-term potentiation [27]. A common single-nucleotide polymorphism in the BDNF gene, a methionine (Met) substitution for valine (Val) at codon 66 (Val66Met), has been associated with reduced regional brain volumes as well as poorer cognitive performance [28]. Increasing BDNF level can improve memory and learning skills in rats [29]. Decreased or low BDNF levels have been associated with cognitive impairment and depression [30]. Therefore, our findings in the association of BDNF with cognition are consistent with the body of current literature.

Limitations

There are some limitations of the present study. First, this is a single-center study, the result cannot be generalized to the general population. Second, it is a retrospective study, and several aphasia battery results had missing data that we couldn't use. Third, the sample size is small. Forth, this study examined the association of serum BDNF level with functional outcome of aphasia, but without analysis of Single Nucleotide Polymorphism (SNF) of BDNF. Further study with a large sample size and combination of genetic analysis would be warranted to confirm the findings.

Conclusion

This study investigated the relationship between BDNF level and cognitive-linguistic outcomes in post-stroke aphasia patients. The findings may provide insight into the biological mechanism of recovery in post-stroke aphasia and may help to develop personalized treatment plans.

Conflicts of Interest

No conflicts of interest have been reported by the authors or by any individuals in control of the content of this article.

The study has been presented as an abstract for at Annual Assembly of American Academy of Physical Medicine and Rehabilitation in October 2018.

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